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- 7-Acylamino-3-substituted cephalosporanic acid derivatives, processes for their preparation, pharmaceutical compositions containing them; their starting compounds and their preparation.
- 57 7-acylamino-3-substituted cephalosporanic acid derivetives of the formula:

in which RI is a group of the formula:

wherein R4 is lower alkyl and

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R⁵ is amino or a protected amino group, R2 is lower alkoxymethyl, lower alkylthiomethyl or lower alkenylthiomethyl,

R' is carboxy or a protected carboxy group, and A is lower alkylene which may have certain substituents

and pharmacautically acceptable sait thereof and procasses for their preparation and also a pharmaceutically omposition comprising, as an effective ingredient, the above compound in association with phermaceutically acceptable carriers. The invention also relates to the starting
 compounds

7- ACYLAMINO - 3- SUBSTD.

CEPHALOSPORIN DERIVS. + USEFUL

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MEDICING AND VETERINARY

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TITLE MODIFIED

7-ACYLAMINO-3-SUBSTITUTED CEPHALOSPORANIC ACID DERIVATIVES, PROCESSES FOR THEIR PREPARATION PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR STARTING COMPOUNDS The present invention relates to novel 7-acylamino-3-substituted cephalosporanic acid derivatives and pharmaceutically acceptable salts thereof.

antimicrobial activity, to processes for the preparation More particularly, it relates to novel 7-acylaminothereof, to a pharmaceutical composition comprising the same, and to a method of using the same therapeutically in the treatment of infectious diseases in human being pharmaceutically acceptable salts thereof, which have 3-substituted cephalosporanic acid derivatives and and animals, 10

poranic acid derivatives and pharmaceutically acceptable is to provide novel 7-acylamino-3-substituted cephalos-Accordingly, one object of the present invention

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salts thereof, which are highly active against a number antimicrobial agents, especially oral administration of pathogenic microorganisms and are useful as

acylamino-3-substituted cephalosporanic acid derivatives Another object of the present invention is to provide processes for the preparation of novel 7and salts thereof.

cephalosporanic acid derivatives and pharmaceutically A further object of the present invention is to provide a pharmaceutical composition comprising, as active ingredients, said 7-acylamino-3-substituted acceptable salts thereof.

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Still further object of the present invention is to provide a method of using said 7-acylamino-3-substituted acceptable salts thereof in the treatment of infectious cephalosporanic acid derivatives and pharmaceutically diseases by pathogenic microorganisms in human being and animals.

The object 7-acylamino-J-substituted cephalosporanic acid derivatives are novel and can be represented by the following general formula: 20

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$$R^{2}-A-CONH \longrightarrow S \qquad (I)$$

in which
$$R^1$$
 is a group of the formula: R^4SO_2NH or R^5H or R^5H

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R is carboxy or a protected carboxy group, and R² is lower alkoxymethyl, lower alkylthiomethyl or lower alkenylthiomethyl, wherein R^4 is lower alkyl and R^5 is amino or a protected amino group,

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"N~OR⁶, wherein R⁶ is hydrogen, lower alkenyl, lower alkynyl, lower alkyl or lower alkyl subof amino, a protected amino group, hydroxy, group, amino, a protected amino group, and is lower alkylene which may have a substituent selected from the groups consisting stituted by one or more substituent(s) se lected from carboxy, a protected carboxy oxo and a group of the formula: heterocyclic group.

also included within the scops of the present invention. and double bond in those molecules and such isomers are In the object compounds (I) and the corresponding mentioned below, it is to be understood that there may and geometrical isomers due to asymmetric carbon atom be one or more stereoisomeric pair(s) such as optical starting compounds (II) to (IV) in Processes 1

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compounds and the starting compounds, it is to be noted , wherein R^1 and R^6 are each as defined isomer means one geometrical isomer having the partial isomer, anti isomer and a mixture thereof, and the syn With regard to geometrical isomers in the object means a group of the formula: "C=NAOR", include syn that, for example, the object compounds, wherein A structure represented by the following formula:

having the partial structure represented by the followand the anti isomer means the other geometrical isomer above, ing formula:

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 $R^{1}\text{-}C^{2}$, wherein R^{1} and R^{6} are each as defined $R^{6}\text{-}O\text{-}N$

Regarding the other object and starting compounds as mentioned above, the syn isomer and the anti isomer

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can also be referred to the same geometrical isomers as illustrated for the compounds (I).

ethanolamine salt, triethanolamine salt, dicyclohexylamine salt such as a salt with an inorganic base, for example, a salt with a basic or acidic amino acid (e.g. arginine, carboxylic or sulfonic acid addition salt (e.g. formate, sulfonate, benzenesulfonate, p-toluenesulfonate, etc.); an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, and may include a salt with a base or an acid addition (e.g. triethylamine salt, pyridine salt, picoline salt, acetate, trifluoroacetate, maleate, tartrate, methaneaspartic acid, glutamic acid, etc.); an intermolecular Suitable pharmaceutically acceptable salts of the object compounds (I) are conventional non-toxic salts salt, N,N'-dibenzylethylenediamine salt, etc.) etc.; magnesium salt, etc.), an ammonium salt; a salt with an inorganic acid addition salt (e.g. hydrochloride, an organic base, for example, an organic amine salt hydrobromide, sulfate, phosphate, etc.); an organic

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may include 1-lower alkylpyridinium lower alkylsulfate pyridinium ethylsulfate, etc.), 1-lower alkylpyridinium case that heterocyclic group in R⁶ in the compounds (I) halide (e.g. 1-methylpyridinium fodide, etq.) and the The said intermolecular quaternary salt can be formed in case that the heterocyclic group in R ⁶ in the com-The said intramolecular salt can be formed in $^{
m 3}$ is carboxy, and suitable intramolecular salt may pounds (I) contains nitrogen atom(s) (e.g. pyridyl, etc.), and suitable intermolecular quaternary salt contains nitrogen atom(s) (e.g. pyridyl etc.) and include 1-lower alkylpyridinium carboxylate (e.g. 1-methylpyridinium carboxylate, 1-ethylpyridinium or intramolecular quaternary salt, and the like. (e.g. 1-methylpyridinium methylsulfate, 1-ethyllike. 35

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1-isopropylpyridinium carboxylate, 1-butylpyridinium carboxylate, 1-propylpyridinium carboxylate, carboxylate, etc.); and the like

According to the present invention, the object compounds (I) and the pharmaceutically acceptable salts thereof can be prepared by the processes as illustrated by the following reaction schemes.

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(continued to the next page)

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(6) Process 6;

R¹-A³-CONHTS Reduction R¹-A⁴-CONHTS

Removal of R¹-A²-CONH
the amino
protective
group in A
R³

 $R^{1-A} - CONH \longrightarrow R^{2} \xrightarrow{\text{R}} R^{2} \xrightarrow{\text{R}} R$

(2) Process 2;

(I-h)

(I-g)

or a salt thereof

or a salt thereof

or a salt thereof

or a salt thereof

(7) Process 7:

10 (3) Process 3:

 $R_a^{1-A-CONH}$

or a salt thereof

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(4) Process 4:

Removal of Rb-A-CONH S the aminoprotective of group for R3 R3

(I-d) or a salt thereof

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 x^{1} -CH₂COA⁵CONH x^{1} -R² x^{2}

(11)

or a salt thereof

(8) Process 8:

R1-A-CONH

or a salt thereof

R¹-A⁶-CONH S Removal of the R¹-A⁷-CONH S tive group of the A⁶-A⁷-CONH S tive group of the A⁸-A⁷-CONH S To H

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or a salt thereof

or a salt thereof

(-I -e)

or a salt thereof

or a salt thereof

(continued to the next page)

(5) Process 5:

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or a salt thereof

or a salt thereof

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(1-f)

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(9) Process 9:

or a salt thereof

or a salt thereof

(11) Process 11:

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$$R^{1}-A^{10}$$
. CONHIPTS (R⁷)₂SO₄ (VII) $R^{1}-A^{11}$. CONHIPTS (A)

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$$R^{1-A^{11}-COMH} \longrightarrow R^2 \longrightarrow R^2 \longrightarrow R^{1-A^{12}-COMH} \longrightarrow R^2$$

10 in which
$$R^1$$
, R^2 , R^3 , R^5 and A a above,

above,
$$R_{\mathbf{a}}^{\mathbf{l}}$$
 is a group of the formula:

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wherein R^{B} is a protected amino group,

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H₂N
$$\neq$$
 N₂H

$$R_a^3$$
 is a protected carboxy group,

$$R_{b}^{3}$$
 is lower alkoxycarbonyl substituted by protected amino and protected carboxy groups,

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or a salt thereof

$$R_{c}^{3}$$
 is lower alkoxycarbonyl substituted by amino and carboxy,

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a group of the formula "N \sim OR 6 , wherein R⁶ is as defined above,

is lower alkylene having a group of the formula: "N $^{\rm C}$ 0R, wherein R $^{\rm G}$ is lower alkyl

is lower alkylene having a group of the formula: "N \sim OR," wherein R is lower alkyl substituted by a protected carboxy group,

protected amino and protected carboxy groups alkoxycarbonyl(lower)alkyl substituted by or lower alkyl substituted by protected is lower alkylene having a group of the formula: "N \sim OR $_c^6$, wherein R_c^6 is lower. amino and protected carboxy groups, substituted by carboxy,

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is lower alkylene having a group of the formula: "N 6 OV wherein 6 O is lower alkoxycarbony1(lower)alkyl substituted by amino and carboxy or lower alkyl substituted by amino and carboxy,

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formula: "N~ORf, wherein Rf is lower alkyl formula: $=N \sim 0R_{\rm e}^6$, wherein $R_{\rm e}^6$ is lower alkyl substituted by a group of the formula: A^{ll} is lower alkylene having a group of the A 10 is lower alkylene having a group of the substituted by a group of the formula:

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5.

R7-50,0

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wherein R⁷ is as defined above,

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A¹² is lower alkylene having a group of the formula: "N \sim OR $_g^6$, wherein R $_g^6$ is lower alkyl substituted by a cation of the formula: wherein R^{T} is as defined above, and

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 $\mathbf{x}^{\mathbf{l}}$ is halogen.

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(IV) used in Processes 1 and 7 are new and can be Some of the starting compounds (II), (III) and

represented by the following formula:

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in which R^{A} is amino or a protected amino group, Rb' is lower alkenyl,

R3 is as defined above, X is -S- or -S0-, and

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and a salt thereof.

the same as those exemplified for the object compounds (I). Suitable salts of the above starting compound are The starting compound thus formulated and other starting compounds can be

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(continued to the next page)

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Preparation of some of the starting

(B) Process B:

compounds (III)

R1-A3-RC

(III-a)

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prepared, for example, from the known compounds by the methods in the following reaction schemes, and others can be prepared in a similar manner thereto or in a conventional manner.

- Preparation of some of the starting compounds (II) Process A: 3
- R^b-SH (VIII) or its reactive derivative at the mercapto group (Process A-1)

- or a salt thereof (II-b) Reduction

or a salt thereof

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(II-a)

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or a salt thereof

(III-b)

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Introduction of the

group (Process B-3)

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amino-protective

(1111-c)

Ra-A2-RC

(Process B-2)

Reduction

R1-A13-RC

R⁶ONH₂ (IX) or a salt thereof

(Process B-1)

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- (Process A-2) Removal of the amino-protective group for R^a (Process A-3)

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- - or a salt thereof (b-11)

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 $R_a^1 - A^1 - R^C$

(h-III)

or a salt thereof

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(J-III)

 $R_b^{1-A^2-R^c}$

- - (II-c)
- - or a salt thereof
- Removal of the carboxy-protective group (Process B-4) Introduction of the amino-protective Removal of the carboxy-protective group (Process B-5) dnoug R_b^1 - A^2 ∞ (g-III)

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 $R_a^{1-A^{1}}$ - ∞ 01

or a salt thereof

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- (Process B-6)
- or a salt thereof (III-e)

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(b) Process b: Preparation of some of the

compounds (II)

Preparation of some of the starting compounds (IV) Process C: <u>.</u>

$$ri$$
 x^1 - $GI_2 COA^5 COA^6I$ S OXY OXY

Lower alkancl substituted by a protected amino and a protected carboxy groups (XII)

(Process D-1)

E00H

$$x^{1}$$
-Cr₁₂CoA⁵COA⁸I $\xrightarrow{R^{2}}$ R²

$$x^2$$
- $cH_2 ca x^5 ca x^6 | x^5$

or its reactive derivative at the amino group or a salt thereof

(IV-a)

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or a reactive derivative at the carboxy group or a salt thereof

(II-e)

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(II-f)

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(II-g)

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(Process E-2)

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(III-j)

in which
$$R_a^1$$
, R_b^1 , R^2 , R^3 , R_b^3 , R^6 , and X^1 are each as defined a

$$R_a^1$$
, R_b^1 , R^2 , R^3 , R^6 , R^6 , A^1 , A^2 , A^3 , A^5 and X^1 are each as defined above,

$$R^{a}$$
 is a protected amino group, R^{b} is lower alkyl or lower alkeny

f is a conventional group which is capable to be replaced by the residue (-
$$SR^b$$
) of the compound of the formula:

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Removal of the carboxy, protective group for R

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a salt thereof

or

(III-k)

(Process E-4)

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Preparation of some of the reagent

Process F:

(F)

or a salt thereof

(1111-1)

used in Process B-1

(continued to the next page)

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(A-VIX)

(Process F-1)

H₂N-0-R⁶ (XIV.c)

phthaloyl group (Process F-2)

Removal of the

derivative at the hydroxy group

or a reactive

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(XIV-a) HO-R⁶

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or a salt thereof

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The term "lower" in the present specification is intended to mean a group having 1 to 6 carbon atoms, unless otherwise indicated.

isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, Suitable "lower alkyl" group may include straight hexyl and the like, in which the preferred one is or branched one such as methyl, ethyl, propyl, $c_1 - c_3$ alkyl.

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and the like, in which the preferred one is $\mathsf{C}_{\mathsf{7}} extsf{-}\mathsf{C}_{\mathsf{5}}$ alkenyl. 1-(or 2- or 3- or 4- or 5-)hexenyl, 2-methyl-2-propenyl, Suitable "lower alkenyl" group may include straight 1-(or 2- or 3-)butenyl, 1-(or 2- or 3- or 4-)pentenyl, or branched one such as vinyl, 1-propenyl, allyl,

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and the like, in which the preferred one is C_2 - C_5 alkynyl. Suitable "lower alkynyl" group may include straight 2-(or 3- or 4-)pentynyl, 2-(or 3- or 4- or 5-)hexynyl, or branched one such as propargyl, 2-(or 3-)butynyl,

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the like, in which the preferred one is C_1 - C_3 alkoxymethyl. alkoxy such as methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, pentyloxymethyl, hexyloxymethyl, and methyl group substituted by straight or branched lower group may include a Suitable "lower alkoxymethyl"

a methyl group substituted by straight or branched lower Suitable "lower alkylthiomethyl" group may include propylthiomethyl, isobutylthiomethyl, pentylthiomethyl, hexylthiomethyl, and the like, in which the preferred alkylthio such as methylthiomethyl, ethylthiomethyl, one is C,-C,alkylthiomethyl.

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alkenylthio such as vinylthiomethyl, lıpropenylthiomethyl, Suitable "lower alkenylthiomethyl" group may include a methyl group substituted by straight or branched lower 1-(or 2- or 3-)butenylthiomethyl, 1-(or 2- or 3- or 4-)pentenylthiomethyl, 1-(or 2- or 3- or 4-)hexenylthiomethyl, and the like, in which the preferred one is allylthiomethyl, 2-methyl-2-propenylthiomethyl, C2-C5alkenylthiomethyl.

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amino group substituted by a conventional amino-protective benzhydry1, trity1, etc.), lower alkoxycarbony1(lower)compounds, for example, acyl as mentioned below, mono-Suitable "protected amino group" may include an group which is used in penicillin and cephalosporin (or di or tri)phenyl (lower) alkyl (e.g. benzyl, 707

methylene (e.g. dimethylaminomethylene, etc.), etc. arbony1-1-propen-2-y1, etc.), di (lower) alkylaminoalkylidene or its enamine tautomer (e.g. 1-methoxy-

acyl substituted with aromatic or heterocyclic group(s). Suitable "acyl" may include an aliphatic acyl, an aromatic acyl, a heterocyclic acyl and an aliphatic

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isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, unsaturated, acyclic or cyclic ones, such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, The aliphatic acyl may include saturated or

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alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl, etc.), erc.), lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl, (C_3-C_7) -cycloalkanecarbonyl (e.g. cyclohexanecarbonyl, propanesulfonyl, etc.), lower alkoxycarbonyl (e.g. butoxycarbonyl, tert-butoxycarbonyl, etc.), lower methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, etc.), amidino, and the like.

The aromatic acyl may include aroyl (e.g. benzoyl, toluoyl, xyloyl, etc.), arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.), and the like

The heterocyclic acyl may include heterocycle-2

carbonyl (e.g. furoyl, thenoyl, nicotinoyl, isonicotinoyl, thiazolylcarbonyl, thiadiazolylcarbonyl, tetrazolylcarbonyl, etc.), and the like.

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The aliphatic acyl substituted with aromatic group(s) phenylpropionyl, phenylhexanoyl, etc.), phenyl(lower)carbonyl, etc.), phenoxy(lower)alkanoyl (e.g. phenoxy alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxymay include phenyl(lower)alkanoyl (e.g. phenylacetyl, acetyl, phenoxypropionyl, etc.), and the like. 20 15

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The aliphatic acyl substituted with heterocyclic group(s) may include thienylacetyl, imidazolylacetyl, thiadiazolylacetyl, thienylpropionyl, thiadiazolyl; furylacetyl, tetrazolylacetyl, thiazolylacetyl,

propionyl; and the like. 52

isopropylthio, butylthio, pentylthio, hexylthio, etc.), fluorine), lower alkoxy (e.g. methoxy, ethoxy, propoxy, hexyl, etc.), halogen (e.g. chlorine, bromine, lodine, These acyl groups may be further substituted with (e.g. methyl, ethyl, propyl, isopropyl, butyl, pentyl, isopropoxy, butoxy, pentyloxy, hexyloxy, etc.), lower one or more suitable substituents such as lower alkyl substituent(s) may be mono (or di or tri)halo(lower). nitro and the like, and preferable acyl having such alkylthio (e.g. methylthio, ethylthio, propylthio, 35

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alkanoyl (e.g. chloroacetyl, bromoacetyl, dichloroacetyl, methoxycarbonyl, 2,2,2-tri-chloroethoxycarbonyl, etc.), trifluoroacetyl, etc.), mono (or di or tri)halo(lower)alkoxycarbonyl (e.g. chloromethoxycarbonyl, dichloronitro (or halo or lower alkoxy)phenyl(lower)alkoxy-

carbonyl, methoxybenzyloxycarbonyl, etc.), and the like. carbonyl (e.g. nitrobenzyloxycarbonyl, chlorobenzyloxy-

Suitable "protected carboxy group" may include an esterified carboxy group which is conventionally used in pentcillin or cephalosporin compounds at their 3rd or 4th position thereof. 07

2,2,2-trichloroethyl ester, etc.), lower alkanoyloxy(lower)-(or di or tri)phenyl(lower)alkoxycarbonyl substituted lower ethyl ester, propyl ester, isopropyl ester, butyl ester, protected amino and protected carboxy substituted lower alkyl ester such as lower alkoxycarbonylamino and monogroup" may include lower alkyl ester (e.g. methyl ester benzhydryloxycarbonylethyĺ, 3-tert-butoxycarbonylaminoester (e.g. ethynyl ester, propynyl ester, etc.), lower substituted lower alkyl ester (e.g. 2-amino-2-carboxyethoxymethyl ester, isopropoxymethyl ester, l-methoxypentyl ester, hexyl ester, etc.), lower alkenyl ester isopropylthiomethyl ester, etc.), amino- and carboxy-(e.g. vinyl ester, allyl ester, etc.), lower alkynyl 3-benzhydryloxycarbonylpropyl, etc.), mono(or di or Suitable "ester moiety" in "esterified carboxy alkoxy(lower)alkyl ester (e.g. methoxymethyl ester, tri)halo(lower)alkyl ester (e.g. 2-iodoethyl ester, ester, ethylthiomethyl ester, ethylthioethyl ester ethyl ester, 3-amino-3-carboxypropyl ester, etc.), isobutyl ester, t-butyl ester, pentyl ester, tert-11kylthio(lower)alkyl ester (e.g. methylthiomethyl alkyl ester (e.g. 2-tert-butoxyc.ırbonylamino-2ethyl ester, 1-ethoxyethyl ester, etc.), lower

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1H:1,2,3-triazoly1, 2H-1,2,3-triazoly1, atc.), methylester, valeryloxymethyl ester, pivaloyloxymethy

methyl ester, butyryloxymethyl ester, isobutyryloxy alkyl estor (o.g. acotoxymothyl ester, propionyloxy

ester, benzhydryl ester, trityl ester, bis(methoxyphenyl)di-t-butylbenzyl ester, etc.), aryl ester which may have ester, cumenyl ester, salicyl ester, etc.), heterocyclic methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5tolyl ester, t-butylphenyl ester, xylyl ester, mesityl or more suitable substituent(s) (e.g. benzyl ester, 4di or tri)phenyl(lower)alkyl ester which may have one mesylmethyl ester, 2-mesylethyl ester, etc.), mono(or one or more suitable substituents (e.g. phenyl ester, ester, hexanoyloxymethyl ester, 2-acetoxyethyl ester etc.), lower alkanesulfonyl(lower)alkyl ester (e.g. methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester (e.g. phthalidyl ester, etc.) and the like. 2-propionyloxyethyl ester, 1-acetoxypropyl ester,

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or branched one such as methylene, ethylene, trimethylene, Suitable "lower alkylene" group may include straight propylene, tetramethylene, hexamethylene, and the like, in which the preferred one is C_1 - C_2 alkylene and the most preferred one is methylene.

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Suitable "heterocyclic" group may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an And, especially preferable heterocyclic group may be oxygen, sulfur, nitrogen atom and the like. heterocyclic group such as

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5 or 6-membered) hereromonocyclic group containing 1 pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidinyl, pyrazinyl, unsaturated 3 to 8-membered(more preferably pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, to 4 nitrogen atom(s), for example, pyrrolyl, 30 35

tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.) saturated 3 to 8-membered (more preferably

5 or 6membered)heteromonocyclic group containing 1 to imidazolidinyl, piperidino, piperazinyl, etc.: nitrogen atom(s), for example, pyrrolidinyl,

unsaturated condensed heterocyclic group containing isoindoly1, indoliziny1, benzimidazoly1, quinoly1 l to 4 nitrogen atom(s), for example, indolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.; 2

unsaturated 3 to 8-membered(more preferably 5 or 6-1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, example, oxazolyl, isoxazolyl, oxadiazolyl (e.g. membered)heteromonocyclic group containing 1 to oxygen atom(s) and 1 to 3 nitrogen atom(s), for etc.), etc.; 13

saturated 3 to 8-membered (more preferably 5 or 6membered) heteromonocyclic group containing 1 to oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

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unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc. 30 25

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saturated 3 to 8-membered (more preferably 5 or 6-2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for membered) heteromonocyclic group containing 1 to example, thiazolidinyl, etc.;

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unsaturated 3 to 8-membered (more preferably 5 or 6sulfur atom(s), for example, thienyl, dihydrodithiinyl, membered) heteromonocyclic group containing 1 to 2 etc.,;

unsaturated condensed heterocyclic group containing for example, benzothiazolyl, benzothiadiazolyl, etc.; l to 2 sulfur atom(s) and l to 3 nitrogen atom(s),

unsaturated 3 to 8-membered (more preferably 5 or 6membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.; 10

unsaturated 3 to 8-membered (more preferably 5 or 6membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing l to 2 sulfur atom(s), for example, benzothienyl benzodithiinyl, etc.; unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc. and the like.

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Thus defined heterocyclic group may optionally be substituted by one to ten, same or different, lower alkyl (e.g. methyl, ethyl, etc.); suitable substituent(s) such as:

cyclo(lower)alkenyl (e.g. cyclohexenyl; cyclohexadienyl, lower alkylthio (e.g. methylthio, ethylthio, etc.); lower alkoxy (e.g. methoxy, ethoxy, propoxy, etc.); (lower)alkyl (e.g. cyclopentyl, cyclohexyl, etc.); lower alkylamino (e.g. methylamino, etc.); cyclo-30 25

nitro; carboxy; protected carboxy as aforementioned; etc.); hydroxy; halogen (e.g. chloro, bromo, etc.); (e.g. aminomethyl, aminoethyl, etc.); and the like. amino; protected amino as aforementioned; cyano; sulfo; sulfamoyl; imino; oxo; amino(lower)alkyl

Suitable "lower alkoxycarbonyl(lower)alkyl" group

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may include ethoxycarbonylmethyl, propoxycarbonylmethyl, or 2-ethoxycarbonylethyl, and the like.

Suitable "lower alkoxycarbonyl" moiety may include ethoxycarbonyl, propoxycarbonyl, and the like.

Suitable "halogen" may include chloro, bromo, iodo, and the like.

formula: HS.R^{b.,} may include halogen as exemplified above. Suitable "conventional group which is capable to be replaced by the residue (-S-R $^{
m b}$) of the compound of the

(continued to the next page)

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Suitable "trihalomethyl" may include trichloromethyl, and the like,

Particularly, the preferred embodiment of the symbols "Rl-A-", "R2" and "R3" of the object compounds (I) can be represented as follows.

The symbol "R 1 -A-" can be represented by the formulae:-

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Rl is a group of the formula:

RS #

(more preferably $R^5 \coprod_S \bigcup$

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(e.g. chloroacetamido, dichloroacetamido, acetamido, propionamido, etc.) or monowherein R⁵ is amino or acylamino (more preferably or di- or trihalo(lower)alkanamido lower alkanamido (e.g. formamido, trifluoroacetamido, etc.)],

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or 2- carboxyethyl, 1- or 2- or 3- carboxypropyl, carboxy(lower)alkyl (e.g. carboxymethyl, 1-R6 is lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, etc.),

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methyl, ethoxycarbonylmethyl, tert- butoxycarbonylmethyl lower alkoxycarbonyl(lower)alkyl (e.g. methoxycarbonylbenzyloxycarbonylmethyl, benzhydryloxycarbonylmethyl, tert- butoxycarbonylethyl, etc.) or mono- or di- or esterified carboxy(lower)alkyl [more preferably triphenyl(lower)alkoxycarbonyl(lower)alkyl (e.g. benzhydryloxycarbonylethyl 1 etc.)]; 1 or

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R1-A- , in which 0 Rl is a group of the formula:

(more preferably R5

wherein R⁵ is amino or acylamino [more preferably acetamido, propionamido, etc.)], and lower alkanamido (e.g. formamido,

tert- butoxycarbonylaminomethylene, etc.)], hydroxymethylene methoxycarbonylaminomethylene, ethoxycarbonylaminomethylene, A is methylene, aminomethylene, acylaminomethylene [more preferably lower alkoxycarbonylaminomethylene (e.g. or carbonyl; or

R1-A- , in which <u></u>

Rl is a group of the formula:

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R4SO2MIX

(more preferably R⁴SO₂NI

propyl, isopropyl, butyl, pentyl, etc.), and wherein R^4 is lower alkyl (e.g. methyl, ethyl,

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lower alkoxycarbonylaminomethylene (e.g. methoxycarbonylaminomethylene, ethoxycarbonylaminomethylene, tert- butoxycarbonyl-A is aminomethylene or acylaminomethylene [more preferably aminomethylene, etc.)].

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the symbol "R2" can be represented by:-

lower alkoxymethyl (e.g. methoxymethyl, ethoxymethyl, 35

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The symbol "R3" can be represented by

alkoxycarbonyl (e.g. benzyloxycarbonyl, benzhydryloxycarbonyl, carboxy or esterified carboxy (more preferably lower alkoxy~ butoxycarbonyl, etc.) or mono- or di- or triphenyl (lower)carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, tertphenethyloxycarbonyl, etc.)].

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The processes 1 to 13 for the preparation of the object compounds (I) of the present invention are explained in detail in the following.

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(1) Process 1:

at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or a salt The compounds (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative

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(III) may include the same ones as illustrated for the Suitable salts of the starting compounds (II) and compounds (1);

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Suitable reactive derivative at the carboxy group of as an aldehyde compound (e.g. acetaldehyde, isopentaldehyde, benzaldehyde, salicylaldehyde, phenylacetaldehyde, action of the amino group with a carbonyl compound such example, a silyl derivative formed by the reaction of the compound (II) may include a conventional one, for chlorobenzaldehyde, hydroxynaphthoaldchyde, furfural, the compound (II) with a silyl compound such as bisits tautomeric enamine type isomer formed by the re-(trimethylsilyl)acetamide, trimethylsilylacetamide, etc.; isocyanate; isothiocyanate; Schiff's base or p-nitrobenzaldehyde, m-chlorobenzaldehyde, p-

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ketone, acetylacetone, ethyl acetoacetate, etc.), and (e.g. acetone, methyl ethyl ketone, methyl isobutyl thiophenecarboaldehyde, etc.) or a ketone compound

- Suitable reactive derivative of the compound (III) anhydride, an activated amide, an activated ester, and bromide; a mixed acid anhydride with an acid such as the like, and preferably an acic chloride and acid may include, for example, an acid halide, an acid
 - dibenzylphosphoric acid, halogenated phosphoric acid, acid, phenylphosphoric acid, diphenylphosphoric acid, substituted phosphoric acid (e.g. dialkylphosphoric thiosulfuric acid, sulfuric acid, alkyl carbonate etc.), dialkylphosphorous acid, sulfurous acid, 10
 - aromatic carboxylic acid (e.g. benzoic acid, etc.); 2-ethylbutyric acid, trichloroacetic acid, etc.), carbonate, etc.), aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, (e.g. methyl carbonate, ethyl carbonate, propyl 15
- with a heterocyclic compound containing imino function a symmetrical acid anhydride; an activated acid amide dimethylpyrazole, triazole or tetrazole; an activated ester (e.g. p-nitrophenyl ester, 2,4-dinitrophenyl such as imidazole, 4-substituted imidazole, 20
- (1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, ester, 8-quinoly1 thioester, or an ester with a N-hydroxy compound such as M,N-dimethylhydroxylamine, 1-hydroxy-2-1-hydroxybenzotriazole, 1-hydroxy-6-chlorobenzotriazole, thioester, p-nitrophenyl thioester, p-cresyl thioester, ester, trichlorophenyl ester, pentachlorophenyl ester carboxymethyl thioester, pyridyl ester, piperidinyl mesylphenyl ester, phenylazophenyl ester, phenyl 25 30

Additionally, as a reactive derivative of the compound (III), wherein A is aminomethylene, the compound 35

etc:), and the like.

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of the following formula can also be used.

$$R_{CH}^{1} = C_{C}^{0}$$
 $HM = 0$ (wherein R^{1} is as defined above)

The suitable reactive derivative can optionally be selected from the above according to the kinds of the compounds (II) and (III) to be used practically.

alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal (e.g. lithium, sodium, potassium, etc.), alkaline earth triethylamine, etc.), pyridine compound (e.g. pyridine, metal (e.g. calcium, etc.), alkali metal hydride (e.g. This reaction can be carried out in the presence of an organic or inorganic base such as alkali metal (e.g. calcium hydride, etc.), alkali metal hydroxide sodium hydride, etc.), alkaline earth metal hydride lutidine, picoline, etc.), quinoline, and the like. potassium tert-butoxide, etc.), trialkylamine (e.g. (e.g. sodium hydroxide, potassium hydroxide, etc.), alkoxide (e.g. sodium methoxide, sodium ethoxide, 5 2 20

is preferably carried out in the presence of a condensing of the free acid or a salt in this reaction, the reaction In case that the compound (III) is used in a form aminopropyl)carbodiimide, etc.]; a ketenimine compound N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethyldicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholino ethylcarbodiimide, N-cyclohexyl-N'-(4-biethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, agent such as a carbodiimide compound [e.g. N,N'-(e.g. N,N'-carbonylbis(2-methylimidazole) 35

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0029557 pontamethyloneketene-M-cyclohexylimine, diphenylketenecompounds (e.g. ethoxyacetylene, 8-chlorovinyl-N-cyclohexylimine, etc.); an olefinic or acetylenic ethyl ether), a sulfonic acid ester of N-hydroxy-

benzotriazole derivative [e.g. 1-(4-chlorobenzenesulfonylthionyl chloride, oxalyl chloride, N-ethylbenzisoxazolium pound (e.g. ethyl polyphosphate, isopropyl polyphosphate, salt, N·ethyl-5-phenylisoxazolium-3-sulfonate, a reagent oxy)-6-chloro-1H-benzotriazole, etc.], a combination of N-methylformamide tetrachloride, disulfide or diazenedicarboxylate (e.g. diethyl diazenedicarboxylate, etc.), a phosphorus com-(referred to as so-called "Vilsmeier reagent") formed phosphoryl chloride, phosphorus trichloride, etc.), or the like with a halogen compound such as thionyl rialkylphosphite or triphenylphosphine and carbon by the reaction of an amide compound such as dimethylformamide,

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The reaction is usually carried out in a conventional such as water, acetone, dioxane, acetonitrile, chloroform, solvent which does not adversely influence the reaction tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine, hexamethylphosphoramide, etc., or a mixture chloride, phosphoryl chloride, phosgene or the like. benzene, methylene chloride, ethylene chloride, thereof.

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Among these solvents, hydrophilic solvents may be used in a mixture with water.

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reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

Process 2; 3

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The compound (I-b) or a salt thereof can be prepared by subjecting the compound (I-a) or a salt thereof to removal reaction of the amino-protective group in $A^{\mathbf{1}}$.

Suitable method for this remoyal reaction may

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include conventional one such as hydrolysis, reduction and the like.

(i) For Hydrolysis:

Hydrolysis is preferably carried out in the presence of an acid.

hydrochloric acid, hydrobromic acid, sulfuric acid, etc.), Suitable acid may be an inorganic acid (e.g. an organic acid (e.g. formic acid, acetic acid,

- exchange resin and the like. In case that trifluoroacetic acid is used in this reaction, the reaction is preferably trifluoroacetic acid, propionic acid, benzenesulfonic carried out in the presence of cation trapping agents acid, p-toluenesulfonic acid, etc.), an acidic ion-(e.g. anisole, etc.). 10
 - The acid suitable for this hydrolysis can be selected removed, for example, this hydrolysis can preferably according to the kinds of the protective group to be applied to the amino-protective group for A¹ such as substituted or unsubstituted lower alkoxycarbonyl, substituted or unsubstituted lower alkanoyl. 20
 - ventional solvent which does not adversely influence The hydrolysis is usually carried out in a con-

the reaction such as water, methanol, ethanol, propanol, mixture thereof, and further the above-mentioned acids can also be used as a solvent when they are in liquid. tetrahydrofuran, N,N-dimethylformamide, dioxane or a

The reaction temperature of this hydrolysis is not critical, and the reaction is usually carried out under cooling to at somewhat elevated temperature.

(ii) For Reduction:

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

35 reduction are a combination of a metal (e.g. tin, zinc, Suitable reducing agents to be used in chemical

inon, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

colloidal platinum, platinum oxide, platinum wire, etc.), barium carbonate, etc.), nickel catalysts (e.g. reduced black, palladium oxide, palladium on carbon, colloidal Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, palladium catalysts (e.g. spongy palladium, palladium iron catalysts (e.g. reduced iron, Raney iron, etc.), palladium, palladium on barium sulfate, palladium on catalysts (e.g. reduced cobalt, Raney cobalt, etc.), copper catalysts (e.g. reduced copper, Raney copper, nickel, nickel oxide, Raney nickel, ett.), cobalt Ullman copper, etc.) and the like.

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example, the chemical reduction can preferably be applied to the amino-protective group for A¹ such as halo(lower)alkoxycarbonyl and the like, and catalytic reduction can The reduction manner can be selected according to the kinds of the protective group to be removed, for preferably be applied to that such as substituted or unsubstituted ar(lower)alkoxycarbonyl, and the like. 20 23

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformanide, or a mixture thereof.

Additionally, in case that the above-mentioned acids to also be used as a solvent. Further, a suitable solvent mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a be used in chemical reduction are in liquid, they can to be used in catalytic reduction may be the above-30 35

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mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

The present invention includes, within the scope of the invention, cases that the protected amino group in transformed into free amino group and/or free carboxy $\mathtt{R}^\mathtt{l}$ and/or the protected carboxy group for \mathtt{R}^3 are group, respectively during the reaction.

Process 3: 3

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The compound (I-d) or a salt thereof can be prepared by subjecting the compound (1-c) or a salt thereof to removal reaction of the amino-protective group in R

This reaction is carried out by a conventional method as hydrolysis, reduction, and the like. such 15

reaction conditions (e.g. reaction temperature, solvent, for the removal reaction of the amino-protective group etc.) are substantially the same as those illustrated of the compound (I-a) in Process 2, and therefore are The method of hydrolysis and reduction, and to be referred to said explanation.

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the invention, cases that the protected amino group in A The present invention includes, within the scope of and/or the protected carboxy group(s) for \mathbb{R}^3 and A are transformed into free amino group and/or free carboxy group, respectively during the reaction. 25

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(4) Process 4:

The compound (I-f) or a salt thereof can be prepared removal reaction of the carboxy-protective group for $extsf{R}_{ extsf{a}}^3$. by subjecting the compound (1-e) or a salt thereof to 30

The method of hydrolysis and reduction, and the This reaction is carried out by a conventional method such as hydrolysis, reduction, and the like.

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reaction conditions (e.g. reaction temperature, solvent, for the removal reaction of the amino-protective group etc.) are substantially the same as those illustrated of the compound (I-a) in Process 2, and therefore are to be referred to said explanation.

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of the invention, cases that the protected amino group(s) in R^{\perp} and A and/or the protected carboxy group in A are The present invention includes, within the scope transformed into free amino group(s) and/or a free carboxy group, respectively during the reaction.

Process 5: . S

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The compound (1-e) or a salt thereof can be prepared by introducing a carboxy-protective group into the compound (I-f) or a salt thereof.

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The introducing agent of a carboxy-protective group to be used in this reaction may include a conventional esterifying agent such as an alcohol or its reactive equivalent (e.g. halide, sulfonate, sulfate, diazo compound, etc.), and the like. This reaction can also be carried out in the presence those given in the explanation of Process 1, and can preof a base, and suitable examples thereof are the same as ferably be carried out in the presence of metal iodide (e.g. sodium iodide, etc.).

reaction such as N,N-dimethylformamide, tetrahydrofuran, dioxane, methanol, ethanol, etc., or a mixture thereof. This reaction is usually carried out in a conventional solvent which does not adversely influence the

The reaction temperature is not critical, and the reaction is usually carried out under cooling to at somewhat elevated temperature,

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In case that the alcohol is used as the introducing be carried out in the presence of a condensing agent as agent of a carboxy-protective group, the reaction can 35

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illustrated in Process 1,

Process 6 9

pared by reducing the compound (1-g) or a salt thereof. The compound (I-h) or a salt thereof can be pre-

The reduction can be carried out by a conventional method such as reduction using a reducing agent, catalytic reduction, and the like,

one used for conversion of a carbonyl group to a hydroxy borohydride (e.g. sodium borohydride, potassium borohyd-Suitable reducing agent may include a conventional methyl group such as metal borchydride, for example, alkali ride, sodium cyanoborohydride, etc.), lithium aluminum hydride, etc.; diborane; and the like. 10

The catalyst to be used in the catalytic reduction may include the same ones as exemplified for the reduction in Process 2. This reaction is usually carried out in a convenreaction such as water, methanol, cthanol, tetrahydrotional solvent which does not adversely influence the furan, dioxane; etc., or a mixture thereof.

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reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

Process 7: 3 25

The compound (I-i) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound (V).

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include the same salts with a base for the compounds (I) Suitable salts of the starting compound (IV) may 30

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This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as ethyl acetute, methylene chloride, chloroform, carbon tetrachloride, tetrahydrofuran, dioxane, water, etc., or a mixture thereof

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reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

(8)

by subjecting the compound (I-k) or a salt thereof to removal The compound (I-1) or a salt thereof can be prepared reaction of the catboxy-protective group in \mathtt{A}^{t}

This reaction is carried out by a conventional method such as hydrolysis, reduction, and the like,

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etc.) are substantially the same as those illustrated for the removal reaction of the amino-protective group of the reaction conditions (e.g. reaction temperature, solvent, The method of hydrolysis and reduction, and the compound (I-a) in Process 2, and therefore are to be referred to said explanation. 15

formed into free amino group and/or free carboxy group, \mathtt{R}^{1} and/or the protected carboxy group in \mathtt{R}^{3} are trans-The present invention includes, within the scope thereof, cases that the protected amino group in respectively during the reaction. (continued to the next page)

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(9.) Process 9:

thereof to removal reaction of the amino- and carboxy· prepared by subjecting the compound (I-m) or a salt The compound (I-n) or a salt thereof can be protective groups in R_h.

This reaction is carried out by a conventional method such as hydrolysis, reduction, and the like.

reaction conditions (e.g. reaction temperature, solvent, the compound (I-a) in Process 2, and therefore are to etc.) are substantially the same as those illustrated for removal reaction of the amino-protective group of The method of hydrolysis and reduction, and the be referred to said explanation.

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In this reaction, the amino- and carboxy-protective

groups can be removed separately or at a time. 15

(10) Process 10:

pared by subjecting the compound (I-o) or a salt thereof to removal reaction of the amino- and carboxy-protective The compound (I-p) or a salt thereof can be pre-20

This reaction is carried out by a conventional method such as hydrolysis, reduction, and the like. groups in A⁸.

reaction conditions (e.g. reaction temperature, solvent, the compound (I-a) in Process 2, and therefore are to for removal reaction of the amino-protective group of etc.) are substantially the same as those illustrated The method of hydrolysis and reduction, and the be referred to said explanation. 52

In this reaction, the amino- and carboxy-protective groups can be removed separately or at a time. 30

Process 11: (T T)

The compound (I-k) or a salt thereof can be prepared by introducing a carboxy-protective group into 35

the compound (I-1) or a salt thereof.

reaction temperature, solvent, etc.) are to be referred Process 5, and therefore, the reaction conditions (e.g. This reaction is carried out by substantially the carboxy-protective group into the compound (I-f) in same method as that illustrated for introducing the to said explanation,

(12) Process 12:

pared by reacting the compound (I-q) or a salt thereof The compound (I-r) or a salt thereof can be prewith the compound (VII). 2

This reaction is usually carried out in a convenreaction such as tetrahydrofuran, dioxane, water, etc., tional solvent which does not adversely influence the or a mixture thereof.

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The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature to under heating.

(13) Process 13:

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pared by reacting the compound (I-r) or a salt thereof The compound (I-s) or a salt thereof can be prewith a base, Suitable base used in this Process may include the same ones as those exemplified in Process 1.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, etc., or a mixture thereof.

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reaction is usually cartled out under cooling to warming. The reaction temperature is not critical, and the

purified in a conventional manner, for example, extraction, Processes 1 to 13 as explained above can be isolated and The object compounds (I) obtained according to the

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precipitation, fractional crystallization, recrystallization, chromatography, and the like.

and (XIV-c) are explained in detail in Processes A to F for the preparation of the starting compounds (II-d), (II-g), (III-b) to (III-e), (III-g), (III-£), (IV)

the following.

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The compound (II-b) or a salt thereof can be prepared by reacting the compound (II-a) or a salt thereof with the compound (VIII) or its reactive derivative at the mercapto

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. Suitable salts of the compounds (II-a) and (II-b) may include the same salts with a base as exemplified for the compounds (I).

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Suitable "reactive derivative at the mercapto group" of the compound (VIII) may include salts, with a base as exemplified for the compounds (I); This reaction is preferably carried out in the pregiven in the explanation of Process 1. sence of a base and suitable examples thereof are the same as those 20

such as N,N-dimethylformamide, dimethylsulfoxide, methanol The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction ethanol, chloroform, etc., or a mixture thereof.

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reaction is usually carried out at ambient temperature The reaction temperature is not critical and the to under warming.

Process A-2: 20

pared by reducing the compound (II-b) or a salt thereof. The compound (II-c) or a salt thereof can be pre-

Suitable salts of the compound (II-c) may include the same salts with a base as exemplified for the compounds $\dot{\Xi}$

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silicon halide (e.g. silicon tetrachloride, etc.); excess amount of acid halide such as lower alkanoyl halide (e.g. sulfinyl group to a thio group such as phosphorus halide alkali metal halide (e.g. sodium iodide, etc.) and acid (e.g. phosphorus trichloride, phosphorus pentachloride, The reducing agent to be used in this reaction may acetyl bromide, acetyl chloride, etc.); combination of etc.); stannous halide (e.g. stannous chloride, etc.); anhydride such as halo(lower)alkanoic anhydride (e.g. include a conventional one used for conversion of a trifluoroacetic anhydride, etc.); and the like.

The reaction is usually carried out in the presence of an acid scavenger such as lower alkene (e.g. 2-methyl 2-butene, etc.), lower alkylene oxide (e.g. ethylene oxide, propylene oxide, etc.) and the like. The reaction is usually carried out in a conventional such as chloroform, methylene chloride, tetrahydrofuran, solvent which does not adversely influence the reaction benzene, etc., or a mixture thereof.

reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

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The compound (II-d) or a salt thereof can be priepared by subjecting the compound (II-c) or a salt thereof to Suitable salts of the compound (II-d) may include removal reaction of the amino-protective group for \mathbb{R}^a . the same ones as exemplified for the compounds (I).

Suitable method for this removal reaction may include conventional one such as a combined method comprising iminohalogenation and iminoetherification, optionally followed by hydrolysis, and the like,

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The first and second steps of this method are presolvent for the first step (i.e. iminohalogenation) is ferably carried out in an anhydrous solvent.

for the second step (i.e. iminoetherification) is usually form, diethyl ether, tetrahydrofuran, dioxane, etc., and an.aprotic solvent such as mothylone chloride, chloro-These two

steps and the last step (i.e. hydrolysis step) are most These two the same as those in the above first step. steps are usually conducted under cooling. preferably conducted in one-batch system.

balogenating agent such as phosphorus halo compound Suitable iminohalogenating agents include a

(e.g. phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, etc.), thionyl chloride, phosphorus tribromide, phosphorus pentabromide, phosgene, and the like. 20

isopropanol, butanol, etc.) or the corresponding alkanol Suitable iminoetherifying agent may be an alcohol having alkoxy (e.g. 2-methoxyethanol, 2-ethoxyethanol, such as an alkanol (e.g. methanol, ethanol, propanol, etc.), and alkoxide of metal such as alkali metal,

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alkaline earth metal (e.g. sodium methoxide, potassium

ethoxide, magnesium ethoxide, lithium methoxide, etc.), and the like. 20

Thus obtained reaction product is, if necessary, hydrolyzed in a conventional manner.

pouring the reaction mixture into water or a hydrophilic moistened or admixed with water, and if necessary, with addition of an acid or base as exemplified in Processes solvent such as alcohol (e.g. methanol, ethanol, etc.) The hydrolysis is preferably carried out at ambient temperature or under cooling, and proceeds simply 25

Process B-l:

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The compound (III-b) can be prepared by reacting the compound (III-a) with the compound (IX) or a salt thereof.

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Suitable sait of the compound (IX) may include the sume one as exemplified for the compounds (I).

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This reaction is preferably carried out in the presence of a base as exemplified in Process 1.

reaction such as water, dioxane, tetrahydrofuran, etc., This reaction is usually carried out in a conventional solvent which does not adversely influence the or a mixture thereof.

reaction is usually carried out under cooling to warm-The reaction temperature is not critical and the 2

Process B-2:

The compound (III-c) or a salt thereof can be prepared by reducing the compound (III-b) 15

Suitable salts of the compound (III-c) may include the same acid addition salt as exemplified for the compounds (1). The reduction can be carried out by a conventional method such as chemical reduction, catalytic reduction, and the like. 70

temperature, solvent, etc.) are substantially the same reduction, and the reaction conditions (e.g. reaction as those illustrated for Process 2, and therefore are The method of chemical reduction and catalytic to be referred to said explanation.

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Process B-3:

ing an amino-protective group into the compound (III-c) The compound (III-d) can be prepared by introducor a salt thereof. 30

The introducing agent of an amino-protective group acyl group as aforementioned or its reactive derivative to be used in this reaction may include a conventional acylating agent such as the corresponding acid to the

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tert-butoxycarbonyloxyimino-2-phenylacetonitrile, etc.), alkyl ketone substituted by lower alkoxycarbonyl (e.g. alkoxycarbonyloxyimino-2-phenylacetonitrile (e.g. 2lower alkyl acetoacetate, for example, methyl aceto-(e.g. acid halide, acid anlydride, etc.), 2-lower acetate, etc., etc.), and the like.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, tetrahydrofuran, dioxane, etc., or a mixture thereof.

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the same as those given in the explanation of Process 1. presence of a base, and suitable examples thereof are This reaction is preferably carried out in the

reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the 15

The compound (III-e) or a salt thereof can be prepared by subjecting the compound (III-d) to removal reaction of the carboxy-protective group

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the same salts with a base as exemplified for the ∞ mpounds (I). Suitable salts of the compound (III-e) may include

This reaction is carried out by a conventional method such as hydrolysis, reduction, and the like.

reaction conditions (e.g. reaction temperature, solvent for the removal reaction of the amino-protective group in Process 2, and therefore are to be referred to said etc.) are substantially the same as those illustrated explanation. Additionally, hydrolysis can be carried The method of hydrolysis and reduction, and the out in the presence of a base, and suitable examples thereof are the same as those in the explanation of 25 30

Process B-5

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prepared by subjecting the compound (III-f) or a salt thereof to removal reaction of the carboxy-protective The compound (III-g) or a salt thereof can be group

those of the compound (III-g) may include the same salts Suitable salts of the compound (III-f) may include the same acid addition salts as exemplified above, and as exemplified for the compounds (I).

The reaction is substantially the same as Process B-4, and therefore, the reaction method, reaction conditions (e.g. reaction temperature, solvent, etc.) are to be referred to said explanation.

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prepared by introducing an amino-protective group into The compound (ill-e) or a salt thereof can be the compound (III-g) or a salt thereof.

This reaction is substantially the same as Process conditions (e.g. reaction temperature, solvent, etc.) B-3, and therefore, the reaction method and reaction ire to be referred to said explanation,

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Process C:

2.5

The compound (IV) or a salt thereof can be prepared tive at the amino group or a salt thereof with the comby reacting the compound (IV-a) or its reactive derivapound (X) or its reactive derivative at the carboxy group or a salt thereof.

the same ones as exemplified for the compounds (I), and Suitable salts of the compound (IV-a) may include those of the compound (X) may include the same salts with a base as exemplified above.

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Process 1, and accordingly, the method, reaction conditions (e.g. reaction temperature, solvent, base, etc.) The reaction is substantially the same method as

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derivative at the carboxy group or a salt thereof with

pared by reacting the compound (II-e) or a reactive

lower alkanol substituted by protected amino and pro-

tected carboxy groups (XII).

The compound (11-f) or a salt thereof can be pre-

Suitable salts of the compounds (II-e) and (II-f)

may include the same ones as exemplified for the com-

pounds (I).

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Suitable reactive derivative at the carboxy group

of the compound (ii-e) may include the same ones as

are to be referred to said explanation.

In this process, carbonyl equivalents, for example, group by a conventional method (e.g. hydrolysis, etc.) alkylene having oxo, can also be used in this reaction and such acetal can easily be transformed into the oxo acetal of the compound (X), wherein A^{S} is lower after the reaction.

(continued to the next page)

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reaction temperature, solvent, etc.) are to be referred Process 5, and therefore, the reaction conditions (e.g. This reaction is carried out by substantially the carboxy-protective group into the compound (I-f) in same method as that illustrated for introducing the the compound (III) in Process 1. to said explanation.

Process D-2: 20

pared by subjecting the compound (II-f) or a salt thereof to removal reaction of the amino-protective group for $\mathbb{R}^{\mathbf{a}}$. The compound (II-g) or a salt thereof can be pre-

Suitable sait of the compound (II-g) may include the same ones as exemplified for the compounds (I).

same method as that illustrated for removal reaction of This reaction is carried out by substantially the the amino-protective group of the compound (II-c) in (e.g. reaction temperature, solvent, etc.) are to be Process A-3, and therefore, the reaction conditions referred to said explanation.

Process E-1:

the compound (III-h) with hydroxylamine or a salt thereof. The compound (111-1) can be prepared by reacting 35

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Suitable salt of hydroxylamine may include the same acid addition salt as exemplified for the compounds (1).

the reagent, the reaction can usually be carried out in In case that the salt of hydroxylamine is used as the presence of a base such as those illustrated in Process 1.

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The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as methanol, ethanol, etc., or a mixture thereof.

reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

Process E-2:

active derivative at the carboxy group or a salt thereof. the compound (III-i) with the compound (XIII) or a re-Suitable salt of the compound (XIII) may include The compound (III-j) can be prepared by reacting 15

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the same salt with a base as exemplified for the compounds

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Suitable reactive derivative at the carboxy group of the compound (XIII) may include the same ones as illustrated for the compound (III) in Process 1.

This reaction is carried out by substantially the same method as Process 1, and therefore, the reaction conditions (e.g. reaction temperature, solvent, etc.) are to be referred to said explanation. 52

Process E-3:

pared by reacting the compound (III-j) or a salt thereof The compound (III-k) or a salt thereof can be prewith ammonia. 30

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the same acid addition salt as exemplified for the com-Suitable salt of the compound (III-k) may include pounds (I). This reaction can be carried out in the absence of

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reaction is usually carried out in the absence of a solor in the presence of a solvent which does not adversely influence the reaction such as dioxane, etc., and the

reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

geometrical isomers, it can be transformed into the other In case that the compound (III-k) is one of the isomer in a conventional manner.

Process E-4:

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to removal reaction of the carboxy-protective group for $R^{oldsymbol{c}}.$ pared by subjecting the compound (III-k) or a salt thereof Suitable salt of the compound (III-1) may include the The compound (III-1) or a salt thereof can be pre-

This reaction is carried out by a conventional method same ones as exemplified for the compounds (I).

The method of hydrolysis and reduction, and the such as hydrolysis, reduction, and the like.

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etc.) are substantially the same as those illustrated for the removal reaction of the amino-protective group of the reaction conditions (e.g. reaction temperature, solvent, compound (I-a) in Process 2, and therefore are to be referred to said explanation.

Process F-1:

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The compound (XIV-b) can be prepared by reacting the compound (XIV-a) or a reactive derivative at the hydroxy group with N-hydroxyphthalimide.

Suitable reactive derivative at the hydroxy group may include halide such as chloride, bromide, and the This reaction is preferably carried out in the presence of a base as exemplified in Process 1. In case that the compound (XIV-a) is used in a free

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presence of a condensing agent as exemplified in Process form, the reaction can usually be carried out in the

reaction such as tetrahydrofuran, N.N-dimethylformamide, This reaction is usually carried out in a conventional solvent which does not adversely influence the etc., or a mixture thereof.

reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

Process F-2:

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The compound (XIV-c) or a salt thereof can be prepared by subjecting the compound (XIV-b) to removal reaction of the phthaloyl group.

the same acid addition salt as exemplified for the com-Suitable salt of the compound (XIV-c) may include pounds (I).

1:

This reaction is carried out by a conventional method such as hydrolysis, and the like. The method of hydrolysis, and the reaction conditions tially the same as those illustrated for removal reaction (e.g. reaction temperature, solvent, etc.) are substanof the amino-protective group of the compound (I-a) in Process 2, and therefore are to be referred to said explanation, 20 25

The starting compounds (II-d), (II-g), (III-b) to and (XIV+c) thus prepared can be isolated in a conventional manner as mentioned for the object compounds of the present invention. (III-e), (III-1), (IV)

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treatment of the reaction mixture therein, in case that reactions in Processes 1 to 13 and A to F or the posttransformed into the other optical and/or geometrical and/or geometrical isomer(s), it may occasionally be the starting or object compounds possess an optical It is to be noted that, in the aforementioned

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isomer(s), and such cases are also included within the scope of the present invention.

position thereof, it may be transformed into its pharma-In case that the object compounds (I) have a free ceutically acceptable salts by a conventional method. carboxy group or free amino group at the 4th or 7th

novel and exhibit high antimicrobial activity, inhibiting the growth of a wide variety of pathogenic microorganisms including Gram-positive and Gram-negative microorganisms and are useful as antimicrobial agents, especially for The object compounds (I) and the pharmaceutically acceptable salts thereof of the present invention are oral administration, 10

pounds (1), the test data on the in vitro antimicrobial Now in order to show the utility of the object comactivity of some representative compounds (I) of this invention are shown in the following. 15

In vitro Antimicrobial Activity. Test:

Test Compounds

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7-[2-(3-Methanesulfonamidophenyl)-D-glycinamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid 7-[2-(2-Aminothiazol-4-yl)-DL-glycolamido]-3trifluoroacetate (hereinafter referred to as methylthiomethyl-3-cephem-4-carboxylic acid (hereinafter referred to as Compound A) Compound B) No. 1 Š

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7-[2-(3-Methanesulfonamidophenyl)-D-glycinamido]-3-allylthiomethyl-3-cephem-4-carboxylic acid trifluoroacetate (hereinafter referred to as Compound C) ٠ ٧

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7-{2-(3-Methanesulfonamidophenyl)-D-glycinamido}-3-methoxymethyl-3-cephem-4-carboxlic acid (hereinafter referred to as Compound D) ٠ ي

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Test Method

In vitro Antimicrobial activity was determined by the two-fold agar-plate dilution method as described below.

One loopful of an overnight culture of each test strain in Tripticase-soy broth (approximately 10⁸ viable cells per ml) was streaked on heart infusion agar (HIagar) containing graded concentrations of antimicrobial agents, and the minimal inhibitory concentration (NIC) was expressed in term of ug/ml after incubation at 37°C for 20 hours.

Test Results 1

MIC (µg/ml)

Batilus subtilis ATCC 6633	0.78	0.10	0.78	0.39
Staphylococcus aureus 209P.JC-1	1.56	1.56	3.13	1.56
Microorganisms Test compounds	А	8 3	້ນ	۵

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For therapeutic administration, the object compounds (1) and the pharmaceutically acceptable salts thereof of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound, as active ingredients, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade and the like.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, magnesium stearate, terra alba, sucrose, corn starch, talc, stearic acid, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethyleneglycol and the like.

While the dosage of the compounds (I) may vary from and also depend upon the age, conditions of the patient, a kind of diseases, a kind of the compounds (I) to be applied, etc. In general, amounts between 1 mg and about 4,000 mg or even more per day may be administered to a patient. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg, 2000 mg of the object compounds (I) of the present invention may be used in treating diseases infected by pathogenic microorganisms.

The following examples are given for the purpose of illustrating the present invention.

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Preparation of the starting compounds

Preparation

and then dried to give benzhydryl 7-(2-phenylacetamido)-3-chloromethyl-3-cephem-4-carboxylate-1-oxide (25 g) in N,N-dimethylformamide (150 ml) were added triethylamine To a solution of benzhydryl 7-(2-phenylacetamido)aqueous solution of sodium chloride (1.5 1), followed by collecting the precipitated solid by filtration, which was washed with water and diisopropyl ether, (6.42 ml) and 2-propene-1-thiol (8.0 ml), and the The reaction mixture was poured into a saturated 3-allylthiomethyl-3-cephem-4-carboxylate-1-oxide mixture was stirred at 25°C for 3 hours.

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(1H, s), 7.4 (15H, s), 8.40 (1H, d, J-8Hz) dd, J=5Hz, 8Hz), 4.8-5.6 (3H, m), 7.00 I.R. (Nujo1): 1775, 1715, 1644, 1170, 1030 cm⁻¹ (6H, m), 5.0 (1H, d, J*5Hz), 5.90 (1H, NMR 6ppm (DMSO-d₆): 3.00 (2H, d, J=7Hz), 3.6

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Benzhydryl 7. (2-phenylacetamido)-3-methylthiomethylreacting benzhydryl 7-(2-phenylacetamido)-3-chloromethyl-3-cephem-4-carboxylate-1-oxide (13.7 g) was obtained by methanolic methanethiol (15 ml) in substantially the 5-cephem-4-carboxylate-1-oxide (15 g) with 30% same manner as that of Preparation 1.

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I.R. (Nujol): 3300, 1775, 1710, 1650, 1172 1027 cm-1 NMR 6ppm (DMSO-d₆): 1.80 (3H, s), 3.3-4.0 (6H, m), J=5Hz, 8Hz), 7.02 (1H, s), 7.50 (15H, s), 5.02 (1H, d, J=5Hz), 5.93 (1H, dd, 8.40 (1H, d, J*8Hz)

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Preparation

Benzhydryl 7-(2-phenylacetamido)-3-ethylthiomethyl-3-cephem-4-carboxylate-1-oxide (14.1 g) was obtained

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with ethanethiol (4.05 ml) in substantially the same chloromethyl-3-cephem-4-carboxylate-1-oxide (15 g) by reacting benzhydryl 7-(2-phenylacetamido)-3manner as that of Preparation 1.

I.R. (Nujol): 3280, 1776, 1708, 1647, 1172, 1015 cm⁻¹

(2H, q, J*7Hz), 3.5-4.0 (6H, m), 5.02 NMR &ppm (DMSO-d₆): 0.95 (3H, t, J=7Hz), 2.28 (1H, d, J=5Hz), 5.93 (1H, dd, J=5Hz, 8Hz), 7.02 (1H, s), 7.5 (15H, s), 8.43 (1H, d, J*8Hz)

Preparation

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To a solution of benzhydryl 7-(2-phenylacetamido)stirring, and the stirring was continued for an hour. pulverized with diisopropyl ether to give benzhydryl dropwise phosphorus trichloride (20 ml) at 5°C with (200 ml) and dried over anhydrous magnesium sulfate. 7-(2-phenylacetamido)-3-allylthiomethyl-5-cephem-4-The mixture was poured into a mixture of methylene separating out the organic layer, which was washed chloride (200 ml) and water (400 ml), followed by twice with an aqueous solution of sodium chloride 3-allylthiomethyl-3-cephem-4-carboxylate-1-oxide (26 g) in methylene chloride (500 ml) was added After removal of the solvent, the residue was carboxylate (22 g).

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NMR (DMSO-d₆): 3.0 (2H, d. J=7Hz), 3.6 (6H, m), (1H, s), 7.40 (15H, m), 9.10 (1H, d, 5.00 (1H, d, J=511z), 5.67 (1H, dd, JuSHz, 8Hz), 4.8.5.5 (3H, m), 6.90 I.R. (Nujol): 1770, 1715, 1650 cm⁻¹ J=8Hz)

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Preparation 5

To a solution of benzhydryl 7-(2-phenylacetamido)-3-methylthiomethyl.3-cephem-4-carboxylate-l-oxide

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2-methyl-2-butene (5.7 ml), followed by adding dropwise acetyl bromide (5.2 ml) under ice-cooling and stirring over anhydrous magnesium sulfate and then evaporated mixture was adjusted to pH about 5 with an aqueous with an aqueous solution of sodium chloride, dried solution of sodium bicarbonate, washed three times [15.1 g) in methylene chloride (150 ml) was added for half an hour. After addition of water, the under reduced pressure to give benzhydryl 7-[2phenylacetamido)-3-methylthiomethyl-3-cephem-4carboxylate (13.5 g).

(1H, d, J=5Hz), 5.75 (1H, dd, J=5Hz, broad s), 3.66 (2H, broad s), 5.23 8Hz), 6.97 (1H, s), 7.43 (15H, s), NMR 6ppm (DMSO-d₆): 1.83 (3H, s), 3.60 (4H, I.R. (Nujol): 3380, 1785, 1715, 1652 cm⁻¹ 9.17 (1H, d, J=8Hz)

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Benzhydryl 7-(2-phenylacetamido)-3-ethylthiomethyl-3-cephem-4-carboxylate (23 g) was obtained by reacting bromide (10.2 ml) in the presence of 2-methyl-2-butene (11.1 ml) in substantially the same manner as that of benzhydryl 7-(2-phenylacetamido)-3-ethylthiomethyl-3cephem-4-carboxylate-1-oxide (30 g) with acetyl Preparation 5.

NMR 6ppm (DMSO-d₆): 1.00 (3H, t, J=7Hz), 2.33 (2H, q, J=7Hz), 3.56 (6H, broad s), 5.17 (1H, d, J*5Hz), 5.76 (1H, dd, I.R. (Nujol): 3300, 1772, 1701, 1650 cm⁻¹ J=5Hz, 8Hz), 7.00 (1H, s), 9.13 (1H, d, J=8Hz)

Preparation 7

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(100 ml) were added benzhydryl 7-(2-phenylacetamido). (16.1 g) and pyridine (6.3 ml) in methylene chloride To a suspension of phosphorus pentachloride

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bicarbonate until the pH value of the aqueous solution anhydrous magnesium sulfate and evaporated to dryness. ether to give benzhydryl 7-amino-3-allylthiomethyl-3-To the separated methylene separating out the organic layer, it was washed with The residue obtained was pulverized with dissopropyl 3-allylthiomethyl-5-cephem-4-carboxylate (22 g) and nethylene chloride (100 ml) at 5°C, and the mixture To this mixture was added water (10 ml) and hereto, followed by stirring at -10°C for half an an aqueous solution of sodium chloride, dried over After cooling to -20°C, methanol (10 ml) was added chloride was added an aqueous solution of sodium was stirred at the same temperature for an hour, became 5.0, and the mixture was shaken. cephem-4-carboxylate (6.5 g). stirred for 10 minutes.

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d, J=5Hz), 4.5-5.6 (3H, m), 6.91 (1H, s), NMR 6ppm (DMSO-d₆): 2.93 (2H, d, J=7Hz), 3.3-3.7 (4H, m), 5.00 (1H, d, J-5Hz), 5.60 (1H, I.R. (Nujol): 1770, 1710 cm⁻¹ 7.5 (10H, m)

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carboxylate (5.0 g) was obtained by reacting benzhydryl substantially the same manner as that of Preparation 7. Benzhydryl 7-amino-3-methylthiomethyl-3-cephem-4-7-(2-phenylacetamido)-3-methylthiomethyl-3-cephem-4carboxylate (13.5 g) with phosphorus pentachloride (7.74 g), pyridine (3 ml) and methanol (100 ml) in I.R. (Nujol): 1765, 1725 cm⁻¹

broad s), 3.60 (2H, broad s), 4.83,5.13 (2H, ABq, J=SHz), 6.97 (1H, s), 7.40 NMR &ppm (DMSO-d₆): 1.81 (3H, s), 3.52 (2H,

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Preparation 9

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Benzhydryl 7-amino-3-ethylthiomethyl-3-cephem-4-

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benzhydryl 7-(2-phenylacetamido)-3-ethylthlomethyl-3methanol (165 ml) in substantially the same manner pentachloride (12.90 g), pyridinę (5.0 ml) and carboxylate (10.0 g) was obtained by reacting cephem-4-carboxylate (23.0 g) with phosphorus as that of Preparation 7.

ABq, J=5Hz), 7.00 (1H, s), 7.43 (10H, s) NMR &ppm (DMSO-d₆): 0.96 (3H, t, J*7Hz), 2.30 (2H, q, J=7Hz), 3.50 (2H, broad s), 3.60 (2H, broad s), 4.80,5.17 (2H, I.R. (Nujol): 1770, 1720 cm⁻¹

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promine (1.24 g) in methylene chloride (10 ml) at -30°C with stirring, and the stirring was continued at -20°C methylthiomethyl-3-cephem-4-carboxylate (4.44 g) and To a solution of diketene (1.3 ml) in methylene 1-bromoacetoacetyl bromide. This solution was added chloride (10 ml) was added dropwise a solution of dropwise to a solution of benzhydryl 7-amino-3for half an hour to prepare a solution of

with stirring, and the stirring was continued at -10°C trimethylsilylacetamide (5.46 g) in methylene chloride solution of sodium bicarbonate, followed by separating out the organic layer, which was washed with water and for half an hour. After addition of water, the resuldryness to give benzhydryl 7-(4-bromoacetoacetamido). (100 ml) at -30 to -20°C over a period of 5 minutes tant mixture was adjusted to pli 7.5 with an aqueous anhydrous magnesium sulfate, and then evaporated to an aqueous solution of sodium chloride, dried over 3-methylthiomethy1-3-cephem-4-carboxylate (6.0 g).

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5.73 (1H, dd, J=4Hz, 8Hz), 6.86 (1H, s), NMR δ ppm (DMSO- d_6) : 1.77 (3H, s), 3.6 (6H, m), 4.33 (2H, s), 5.15 (1H, d, J=4Hz), 7.3 (10H, m), 9.1 (1H, d, J=8Hz) IR (Nujol) : 1770, 1710, 1625 cm⁻¹

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To a solution of ethyl 2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetic acid (syn isomer)(19 g) in methanol (200 ml) were added 50% formic acid (200 ml) and zinc adjusted to pH 6.5 with 4N aqueous solution of sodium 6 hours. After filtration, the reaction mixture was hydroxide, followed by addition of ethanol (150 ml), (29 g), and the mixture was stirred at 5 to 10°C for water (150 ml). The resultant aqueous solution was evaporated, followed by dissolving the residue in reparation 11

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butoxycarbonyl-2-(2-formamidothiarol-4-yl)glycine (3.3 g). mixture was filtered, followed by removal of the organic acid and then extracted with ethyl acetate. The extract solvent. The remained aqueous solution was washed with was washed with an aqueous solution of sodium chloride, ethyl acetate, adjusted to pH 4 with 10% hydrochloric dried over anhydrous magnesium sulfate and evaporated which was washed with diethyl ether to obtain N-tertto dryness under reduced pressure to give a residue, (18.2 g) and triethylamine (8.0 g): After stirring 2-tert-butoxycarbonyloxyimino-2-phenylacetonitrile at ambient temperature for 24 hours, the reaction

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IR (Nujo1) : 3250, 3180, 1720, 1700, 1670, 1640, 1540, 1510 cm⁻¹

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NAR 6ppm (DMSO-d₆) : 1.40 (9H, s), 5.18 (1H, d, J=8Hz), 7.17 (1H, s), 8.43 (1H, s)

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Preparation 12

dissolved in methylene chloride (700 ml). The solution dried over magnesium sulfate, and then evaporated under acetate at 45°C, and the reaction mixture was stirred triethylamine (15,1 ml), and the reaction mixture was resultant mixture was poured into a saturated aqueous sodium chloride (500 ml). The precipitates were colover magnesium sulfate. The solution was evaporated solution was added N-hydroxyphthallmide (11.7 g) and in vacuo to give an oily product. This oil was diswas washed with a saturated aqueous sodium chloride, was washed with 5% aqueous sodium bicarbonate and a equivalent volume of diphenyl diazomethane in ethyl at the same temperature for an hour. The solution saturated aqueous sodium chloride, and then dried lected by filtration, washed with water, and then stirred at ambient temperature for an hour. The Bromoacetic acid (10.45 g) was dissolved in To the solution was added an solved in N,N-dimethylformamide (60 ml), methanol (30 ml),

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IR (Nujol): 1754, 1730 cm⁻¹ (20.4 g), mp 173-175°C.

reduced pressure to give benzhydryl 2-phthalimidooxyacetate

NMR 6ppm (CDC13,6):4.93 (2H,5),7.0 (1H,5), 7.3 (10H,5), Preparation 13

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were collected by filtration and washed with methylene The precipitates 7.73 (4H, s). methanol (7 ml). The reaction mixture was stirred To a solution of benzhydryl 2-phthalimidooxyadded a solution of hydrazine hydrate (6.08 g) in chloride. The filtrate and the washings were comacetate (10 g) in methylene chloride (100 ml) was bined, adjusted to pH 7.0 with conc. hydrochloric acid, and washed with a saturated aqueous sodium chloride, and then dried over magnesium sulfate. at ambient temperature for an hour.

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evaporated in	hydryl 2-aminooxyacetate (6.0	3320, 1750
evap	ooxy	3320
×8.5	amin	••
lon	1.2-	film]
solution was	hydry	IR (film)

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6ppm (CDC13, 6): 4.33 (2H, s), 5.86 . NMR

(2H, broad s), 7.00 (1H, s), 7.3 (10H,s)

Preparation 14

The separated organic glyoxylic acid (6.0 g) in water (60 ml) and pyridine (6 ml) was added a solution of benzhydryl 2-aminooxy The reaction mixture was stirred at ambient tempera-To a suspension of (2-formamidothiazol-4-yl)ture for 3 hours. To the resultant solution was acetate (9.0 g) in tetrahydrofuran (40 ml). added ethyl acetate (200 ml), 10

a saturated aqueous sodium bicarbonate and a saturated iqueous sodium chloride, and then dried over magnesium formamidothiazol-4-yl)-2-benzhydryloxycarbonylmethoxysulfate. The solvent was distilled off to give 2-(2iminoacetic acid (syn isomer) (13.0 g), mp 143-151°C. layer was washed with 5% hydrochloric acid (100 ml), 20 15

(1H, s), 7.40 (20H, m), 7.56 (1H, s) NMR 6ppm (DMSO-d6) : 5.0 (2H, broad s), 6.97 8.60 (1H, s), 12.77 (1H, broad s) IR (Nujol) : 3150, 1733, 1692 cm

Preparation 15

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minutes. To the reaction mixture was added triethylamine bicarbonate. The aqueous layer was adjusted to pH 2.0 To a solution of 2-benzhydryloxy.carbonylmethoxyadded ethyl acetate (100 ml) and water (100 ml), and isomer)(7.5 g) in tetrahydrofuran (40 ml) was added (5.3 ml) at -10°C, and then the mixture was stirred for 90 min at 0 to 5°C. To the above mixture were adjusted to pH 7.5 with a saturated aqueous sodium imino-2-(2-formamidothlazol-4-yl)acetic acid (syn trifluoroacetic anhydride (7.9 g) at -16°C for 10 with conc. hydrochloric acid and extracted with 33

substance was collected by filtration to give crystalline 2-benzhydryloxycarbonylmethoxyimino-2-[2-(2,2,2ethyl acetate (200 ml). The organic layer was washed over magnesium sulfate. The solvent was removed by with a saturated aqueous sodium chloride and dried n-Hexane was added to the oil and the precipitated evaporation under reduced pressure to give an oil, trifluoroacetamido)thiazol-1-yl]acetic acid (syn isomer) (6.0 g), mp 178-180°C.

NMR 6ppm (DMSO-d6) : 4.98 (2H, s), 6.92 (1H, s), 7.32 (10H, m), 7.69 (1H, s) IR (Nujo1) : 1752, 1726 cm⁻¹

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Preparation of the object compounds

Example.1

followed by extracting with methylene chloride (100 ml). to a solution of benzhydryl 7-amino-3-methylthiomethylglycinamido]-3-methylthiomethyl-3-cephem-4-carboxylate the activated acid. This solution was added dropwise The extract was washed twice with 5% aqueous solution of sodium bicarbonate (50 ml) and an aqueous solution same temperature for 40 minutes to give a solution of 3-cephem-4-carboxylate (3.0 g) in methylene chloride stirring, and the stirring was continued at the same vas added dropwise a solution of ethyl chloroformate with stirring, and the stirring was continued at the (0.91 ml) in tetrahydrofuran (10 ml) at -10 to -7°C After addition of water, the reaction mixture was stirred for half an hour, triethylamine (1.34 ml) in tetrahydrofuran (50 ml) (100 ml) at -30°C over a period of 5 minutes with of sodium chloride, and then dried over anhydrous magnesium sulfate, followed by evaporation under butoxycarbony1-2-(3-methanesulfonamidopheny1)-D-To a solution of N-tert-butoxycarbonyl-2-(3methanesulfonamidophenyl)-D-glycine (3.3 g) and reduced pressure to give benzhydryl 7-[N-terttemperature for an hour.

I.R. (Nujol): 1780, 1710, 1680, 1152 cm⁻¹

NMR & ppm (DMSO-d₆): 1.36 (9H, s), 1.76 (3H, s),

2.98 (3H, s), 3.5-3.8 (4H, m), 5.12
(1H, d, J=5Hz), 5.73 (1H, dd, J=5Hz,

8Hz), 6.93 (1H, s), 7.1-7.4 (14H, m),

9.93 (1H, d, J=8Hz)

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Example

Benzhydryl ?-[N-tert-butoxycarbonyl-2-(3-methanesulfonamidophenyl)-D-glycinamido]-3-ethylthiomethyl-3-cephem-4-carboxylate (5.4 g) was obtained by reacting benzhydryl ?-amino-3-ethylthiomethyl-3-cephem-4-carboxylate (3.08 g) with N-tert-butoxycarbonyl-2-(3-methanesulfonamidophenyl)-D-glycine (5.3 g) in substantially the same manner as that of Example 1.

I.R. (Nujol): 3250, 1780, 1700, 1530, 1490,

1455 cm⁻¹

NMR dppm (DNSO-d₆): 0.98 (3H, t, J=7Hz), 1.38
(9H, s), 2.28 (2H, q, J=7Hz), 2.97
(3H, s), 3.4-3.8 (4H, m), 5.12 (1H, d, J=5Hz), 5.24 (1H, m), 5.73 (1H, dd, J=5Hz), 5.24 (1H, m), 5.73 (1H, dd, J=5Hz, 7Hz), 6.93 (1H, s), 7.0-7.7
(14H, m), 9.89 (1H, d, J=8Hz), 10.43

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Example 3

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NMR $\phi_{\rm DPm}$ (DMSO- d_6): 1.5 (9H, s), 2.3 (2H, broad s), solution was extracted with methylene chloride (50 ml). 3.24 (3H, s), 3.51 (2H, s), 4.15 (2H, s), over anhydrous magnesium sulfate and then treated with To a suspension of tert-butyl 7-amino-3-methoxy. methylene chloride (200 ml) was added water (100 ml), an activated charcoal, followed by evaporation under followed by adjusting to pH about 6 with an aqueous the methylene chloride layer, the remaining aqueous The combined methylene chloride solution was washed methyl-3-cephem-4-carboxylate tosylate (13.1 g) in With an aqueous solution of sodium chloride, dried reduced pressure to give tert-butyl 7-amino-3-I.R. (Nujol): 3370, 1760, 1740, 1710 cm⁻¹ methoxymethyl-3-cephem-4-carboxylate (5.7 g). olution of sodium bicarbonate.

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4.8 (1H, d, J=5Hz); 5.04 (1H, d, J=5Hz) tetrahydrofuran (95 ml) was added dropwise a solution of ethyl chloroformate (2.8 g) in dry tetrahydrofuran with stirring, and stirring was continued at the same temperature for 40 minutes to prepare a solution of (25 ml) at -10 to -7°C over a period of 10 minutes glycine (8.89 g) and triethylamine (2.61 g) in dry On the other hand, to a solution of N-tertbutoxycarbonyl-2-(3-methanesulfonamidophenyl)-Dthe activated acid.

7-[N-tert-butoxycarbonyl-2-(3-methanesulfonamidophenyl). aqueous solution was extracted with methylene chloride. After addition of water (100 ml), the reaction mixture was stirred for half an hour. The methylene chloride To a solution of the compound (5.65 g) obtained D-glycinamido].5-methoxymethyl.3.cephem-4-carboxylate evaporation under reduced pressure to give tert-butyl according to Example 3-(1) in dry methylene chloride activated acid prepared above at -30°C over a period twice with 5% aqueous solution of sodium bicarbonate (100 ml) and an aqueous solution of sodium chloride, layer was separated out therefrom and the remaining The combined methylene chloride solution was washed of 10 minutes with stirring, and the stirring was dried over anhydrous magnesium sulfate, and then (190 ml) was added dropwise the solution of the treated with an activated charcoal, followed by continued at the same temperature for an hour.

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NMR oppm (DMSO-d₆): 1.36 (9H, s), 1.46 (9H, s), 2.97 (3H, s), 3.18 (3H, s), 3.4 (2H, 5.73 (1H, dd, J=5Hz, 8Hz), 6.93-7.43 (1H, d, J=5Hz), 5.24 (1H, d, J=8Hz), broad s), 4.07 (2H, broad s), 5.03 I.R. (Nujol): 3250, 1780, 1710, 1680 cm⁻¹

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(1H, d, J*8Hz), 9.73 (1H, broad s) (4H, m), 7.5 (1H, d, J-8llz), 9.16

The compounds described in the following Examples methanesulfonamidophenyl)-D-glycine in substantially 4 to 7 were obtained by reacting the corresponding 7-aminocephalosporanic acid derivative with 2-(3the same manner as that of Example 3, Example 4 7 - [2 - (3 - Methanesulfonamidophenyl) - D - glycinamido] -I.R. (Nujol): 1758, 1687 (shoulder), 1666, 1144, 3-methylthiomethyl-5-cephem-4-carboxylic acid.

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Example 5

7-[2-(3-Methanesulfonamidopheny1)-D-glycinamido]-I.R. (Nujo1): 3500, 3150, 1780, 1685, 1460 cm⁻¹ 3-ethylthiomethyl-3-cephem-4-carboxylic acid. Example 6

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7-[2-(3-Methanesulfonamidophenyl).D-glycinamido]. I.R. (Nujol): 3500, 3150, 1760, 1685 cm⁻¹ 3-methoxymethyl-3-cephem-4-carboxylic acid.

Example 7

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7-[2-(3-Methanesulfonamidopheny1).D-glycinamido]. 3-allylthiomethyl-3-cephem-4-carboxylic acid trifluoroacetate.

I.R. (Nujol): 1760, 1680, 1600, 1140 cm⁻¹

Example 8

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ether (500 ml), and the precipitated solid was collected A mixture of benzhydryl 7-[N-tert-butoxycarbonylthe reaction mixture was added dropwise to dissopropyl by filtration, washed with diisopropyl ether and then After the reaction, anisole (5.0 ml) in trifluoroacetic acid (20 ml) was dissolved in a mixture of water (50 ml) and ethyl 2-(3-methanesulfonamidophenyl)-D-glycinamido]-3methylthiomethyl-3-cephem-4-carboxylate (6.5 g), After the aqueous layer was stirred at 25°C for 15 minutes. acetate (50 ml).

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followed by removal of ethyl acetate from the aqueous The resultant aqueous solution was adjusted to pH 5, After washing with water (180 ml), elution was carried out with 30% isopropyl alcohol, with an aqueous solution of sodium bicarbonate and subjected to column chromatography using "Diaion separated out, it was washed with ethyl acetate, solution completely under reduced pressure. HP-20" (90 ml).

and the fractions containing the desired compound were

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(continued to the next page)

I.R. (Nujol): 1758, 1687 (shoulder), 1666, 1144, methylthiomethyl-3-cephem-4-carboxylic acid (4.8 g) methanesulfonamidophenyl)-D-glycinamido]-3collected and lyophilized to give 7-[2-(3-974 cm⁻¹ NMR &ppm (D₂O + DCl): 1.98 (3H, s), 3.15 (3H, s), 3.45 (2H, broad s), 3.56 (2H, broad s), 5.12 (1H, d, J=5Hz), 5.30 (1H, s), 5.70 (1H, d, J=5Hz), 7.45 (4H, s)

Example 9 01

presence of anisole (7.4 ml) in substantially the same 7-[2-(3-Methanesulfonamidophenyl)-D-glycinamido]glycinamido]-3-ethylthiomethyl-3-cephem-4-carboxylate 3-ethylthiomethyl -3-cephem-4-carboxylic acid (1.6 g) (3.7 g) with trifluoroacetic acid (7.4 ml) in the butoxycarbonyl-2-(3.methanesulfonamidophenyl)-Dmanner as that of Example 8, mp 188°C (dec.). was obtained by reacting benzhydryl 7-[N-tert-

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NMR &ppm (D,O + DCl): 1.13 (3H, t, J=7Hz), 2.48 I.R. (Nujol): 3500, 3150, 1780, 1685, 1460 cm⁻¹ (2H, q, Ja7Hz), 3.11 (5H, s), 3.3-3.8 (4H, m), 5.30 (1H, s), 5.65 (1H, d, J=5Hz), 7.43 (4H, s)

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Example 10

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The reaction mixture was poured into diisopropyl ether (750 ml), followed by stirring at ambient temperature period of 10 minutes with stirring, and the stirring glycinamido]-3-methoxymethyl-3-cephem-4-carboxylate collected by filtration and washed with diisopropyl for 20 minutes. After the precipitated solid was trifluoroacetic acid (33.75 ml) below 15°C over a butoxycarbonyl-2-(3-methanesulfonamidophenyl)-D-(15 g) in anisole (11.25 ml) was added dropwise was continued at 15 to 20°C for half an hour. To a solution of tert-butyl 7-[N-tert-

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The combined aqueous solution was concentrated "Diaion HP-20" (225 ml), which was washed with water collected and evaporated under reduced pressure, and adjusted to pH about 3.8 with ar aqueous solution of sodium bicarbonate, followed by subjecting to column ether, it was poured into a mixture of ethyl acetate (450 ml) and then eluted with 30% isopropyl alcohol. (100 ml) and water (100 ml) and stirred for a while. and the remaining organic layer was extracted with he fractions containing the desired compound were chromatography using non-ionic adsorption resin methoxymethyl-3-cephem-4-carboxylic acid (4.45 g). The aqueous solution was separated out therefrom, under reduced pressure, and the concentrate was the residue was lyophilized to give 7-[2-(3methanesulfonamidophenyl)-D-glycinamido]-3-

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NMR 6ppm (D, 0 + DC1): 3.13 (3H, s), 3.26 (3H, s), 5.06 (1H, d, J=5Hz), 5.27 (1H, s), 5.73 3.42 (2H, q, J=18Hz), 4.25 (2H, s), I.R. (Nujo1): 3500, 3150, 1760, 1685 cm^{-l} (1H, d, J≓SHz), 7.42 (4H, s)

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Example 11

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hour, followed by adding dropwise to diisopropyl ether. Benzhydryl 7-amino-3-allylthiomethyl-3-cephem-4ashed with diisopropyl ether and then dissolved in The aqueous layer was separated out and washed with carboxylate (3.3 g) and N-tert-buroxycarbonyl-2-(3treated in substantially the same manner at that of A mixture of this oil, trifluoroacetic acid (15 ml) and anisole (15 ml) was stirred at 20°C for half an The presipitated solid was collected by filtration, nixture of water (50 ml) and ethyl acetate (50 ml). methanesulfonamidophenyl)-D-glycine (3:44 g) were diethyl ether, followed by removal of the organic example 1 to give an oily product (6.5 g).

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The resultant aqueous methanesulfonamidophenyl)-D-glycinamido]-3allylthiomethyl-3-cephem-4-carboxylic acid solution was lyophilized to give 7-[2-(3solvent therefrom completely. trifluoroacetate (2 g).

NMR $6ppm (D_2O + DC1): 3.20 (2H, m), 3.23 (3H, s),$ 3.6 (7H, m), 5.2 (lH, d, J*SHz), 5.45 (1H, s), 5.80 (1H, d, J=5Hz), 7.55 I.R. (Nujol): 1760, 1680, 1600, 1140 cm⁻¹ (3H, m)

Example 12

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To a solution of benzhydryl 7-[4-bromoacetoacetamido]ashed twice with an aqueous solution of sodium chloride, 30°C for an hour. The reaction mixture was poured into a mixture of ethyl acetate (100 ml) and water (100 ml), followed by separating out the organic layer, which was with stirring, and the stirring was continued at 28 to dried over anhydrous magnesium sulfate and then evapotetrahydrofuran (30 ml) was added dropwise a solution in tetrahydrofuran (30 ml) and water (24 ml) at 25°C 3-methylthiomethyl.3-cephem-4-carboxylate (6.0 g) in acetamido]-3-methylthiomethyl-3-cephem-4-carboxylate of thiourea (0.85 g) and sodium bicarbonate (0.94 g) rated to give benzhydryl 7-[2-(2-aminothiazol-4-yl)-

NMR 6ppm (DMSO-d₆) : 1.85 (3H, s), 3.3-3.8 (6H, m), J=5Hz, 8Hz), 6.32 (1H, s), 7.00 (1H, s), 5.25 (1H, d, J=5Hz), 5.80 (1H, dd, 7.43 (10H, s), 8.95 (1H, d, J=8Hz) IR (Nujol) : 1773, 1715, 1653 cm⁻¹

Example 13

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carboxylate tosylate (2.0 g) was dissolved in a mixture of acetone (40 ml) and a saturated aqueous solution of tert.Eutyl 7-amino-3-methoxymethyl-3-cephem-4sodium bicarbonate (15 ml), and thereto was added

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13 70 phosphorus oxychloride (0.85 g) and N,N-dimethylformamide 7-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]dryness under reduced pressure to give a residue, which was triturated with dicthyl ether to obtain tert-butyl value of the reaction mixture was maintained at $pH\ 7.0$ extract was washed with 5% aqueous solution of sodium (0.41 g) in tetrahydrofuran (10 ml), at 0 to 5°C over carbonate. After stirring for an hour, the reaction bicarbonate and water, dried and then evaporated to 3-methoxymethyl.3-cephem-4-carboxylate (syn isomer) dropwise a solution of the activated acid, which was The combined mixture was diluted with water (50 ml), followed by During the addition, the pH to 7.5 with a saturated aqueous solution of sodium $_{
m nethoxyiminoacetic}$ acid (syn isomer)(1.06 $_{
m 8}$), prepared from 2-(2-formamidothiazol-4-yl)-2extracting twice with ethyl acetate. period of 10 minutes.

NAR 6ppm (DMSO-d₆) : 1.49 (9H, s), 3.21 (3H, s), 3.28 (2H, broad s), 3.89 (3H, s), 4.1 IR (Nujol) : 3250, 3100, 1790, 1710, 1660 cm⁻¹ (1H, dd, J=SHI, 8HI), 7.36 (1H, s), rzH, s), S.16 (1H, d, J=5Hz), 5.80 8.48 (1H, s), 9.6 (1H, d, J=8Hz), 12.66 (1H, broad s)

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Example 14

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methoxyiminoacetamido]-3-methylthiomethyl-3-cephem-4thiazol-4-yl)-2-methoxyiminoacetic acid (syn isomer) (0.85 g) according to the similar manner to that of cephem-4-carboxylate (0.90 g) with 2-(2-formamidoreacting tert-butyl 7-amino-3-methylthiomethyl-3tert-Butyl 7-[2-(2-formamidorhiazol-4-yl)-2carboxylate (syn isomer)(0.91 g) was obtained by Example 13.

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3.29 (2H, broad s), 3.55 (2H, ABq, J=13Hz), NMR 6ppm (DMSO-d₆) : 1.47 (911, s), 1.97 (3H, s), 3.87 (3H, s), 5.21 (1H, d, J#5Hz), 5.76 (1H, dd, J*5Hz, 8Hz), 7.38 (1H, s), 8.49 (1H, s), 9.66 (1H, d, J-8Hz), IR (Nujo1) : 3250, 3050, 1780, 1690 cm⁻¹ 12.56 (1H, broad s)

15 to 17 were obtained by reacting the 7-aminocephalos-The compounds described in the following Examples according to the similar manner to that of Example 13, poranic acid derivatives with the corresponding, acid

7-[2-(2-Aminothiazo1-4-y1)acetamido]-3methylthiomethyl-3-cephem-4-carboxylic acid IR (Nujol) : 1763, 1654 cm⁻¹

7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid hydrochloride (syn isomer)

IR (Nujol) : 3300, 1780, 1720, 1660, 1640 cm⁻¹

Example 17

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3-methylthiomethyl-3-cephem-4-carboxylic acid (syn isomer) 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-IR (Nujo1) : 5350, 1770, 1670 cm^{-1}

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(3.3 g), trifluoroacetic acid (10 ml) and anisole (10 ml) 1) acetamido] - 3-methylthiomethyl - 3-cephem - 4-carboxylate The remained aqueous solution was poured into a mixture of ethyl acetate (100 ml) and water (100 ml), followed in methylene chloride (10 ml) was stirred at 10°C for The mixture of benzhydryl 7-[2-(2-aminothiazol-4in hour. After benzene (50 ml) was added to the reaction mixture, the trifluoroacetic acid therein was azeotropically removed under reduced pressure.

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separating out the aqueous solution, the organic solvent by adjusting to pH 7.5 with sodium bicarbonate. After reduced pressure, followed by adjusting to pH 3.0 with was removed therefrom by evaporation completely under 104 hydrochloric acid. The precipitated solid was

(2-aminothiazol-4-yl)acetamido]-3-methylthiomethyl-3collected by filtration and then dried to give 7-[2cephem-4-carboxylic acid (0.95 g).

IR (Nujol) : 1763, 1654 cm⁻¹

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3.65 (4H, broad s), 5.17 (1H, d, J=5Hz), 5.67 (1H, dd, J=5Hz, 8Hz), 6.38 (1H, s), NMR 6ppm (DMSO- d_6) : 2.01 (3H, s), 3.48 (2H, s), 9.00 (1H, d, J=8Hz)

Example 19

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in methylene chloride (20 ml) were added trifluoroacetic for 3 hours. After evaporation of the reaction mixture, sodium bacarbonate. The resultant aqueous solution was gradually warmed at 40°C, followed by stirring at 10°C 30 minutes in diethyl ether, and the remained substance acid (4.4 g) and anisole (0.2 ml), and the mixture was methoxymethyl-3-cephem-4-carboxylate(syn isomer)(1.0g) chloride in turn, dried and then evaporated to dryness adjusted to pH 2.0 with diluted hydrochloric acid and under reduced pressure. The residue was stirred for bicarbonate, water and an aqueous solution of sodium methoxymethyl-3-cephem-4-carboxylic acid (syn isomer) washed with a saturated aqueous solution of sodium formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3followed by extracting with an aqueous solution of then extracted with ethyl acetate. The extract was formamidothiazol-4-y1)-2-methoxyiminoacetamido]-3-(20 ml), To a cold suspension of tert-butyl 7-{2-(2vas collected by filtration to give 7-[2-(2o the residue was added ethyl acetate

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broad s), 3.90 (3H, s), 4.19 (2H, s), (1H, s), 9.67 (1H, d, J*8Hz), 12.58 NMR &ppm (DMSO-d₆) : 3.22 (3H, s), 3.55 (2H, 5.17 (1H, d, J=5Hz), 5.81 (1H, dd, J=5Hz, 8Hz), 7.43 (1H, s), 8.51 IR (Nujol) : 3250, 1780, 1660 cm⁻¹ (1H, broad s)

Example 20

according to the similar manner to that of Example 19. nethoxyiminoacetamido]-3-methylthiomethyl-3-cephem-4carboxylate (syn isomer)(0.9 g) with trifluoroacetic acetamido].3-methylthiomethyl-3-cephem-4-carboxylic 7-[2-(2-Formamidothiazol-4-yl)-2-methoxyiminoicid (syn isomer)(0.64 g) was obtained J, reacting acid (5.8 g) in the presence of anisole (0.9 ml) tert-butyl 7-[2-(2-formamidothiazol-4-yl)-2-

NMR бррл (DMSO-d₆) : 1.99 (3H, s), 3.38-4.1 (4H, m), 3.93 (3H, s), 5.25 (1H, d, J=5Hz), 5.79 (1H, dd, J*SHz, 8Hz), 7.45 (1H, s), 8.43 (1H, s), 9.65 (1H, d, J=8Hz), IR (Nujol) : 3250, 1780, 1660 cm⁻¹ 12.68 (1H, broad s)

21 and 22 were obtained by reacting tert-butyl ester of the corresponding cephalosporanic acid derivatives with trifluoroacetic acid in the presence of anisole accord-The compounds described in the following Examples ing to the similar manner to that of Example 19. xample 21 7-[2-(2-Aminothiazol-4-y1)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid hydrochloride (syn isomer)

IR (Nujol) : 3300, 1780, 1720, 1660, 1640 cm⁻¹ Example 22 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid (syn

. IR (Nujol) : 3350, 1770, 1670 cm⁻¹

isomer)

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Example 23

and tetrahydrofuran (2 ml) was added conc. hydrochloric acid to give 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic by filtration, washed with diisopropyl ether and then dried diisopropyl ether, the precipitated crystals were collected acid (syn isomer) (0.52 g) in a mixture of methanol (3 ml) (0.18 g), and the mixture was stirred at 30°C for 4 hours. To a suspension of 7-[2-(2-formamidothiazol-4-yl)-2-3-methoxymethyl-3-cephem-4-carboxylic acid hydrochloride After the reaction mixture was cooled and diluted with (syn isomer) (0.45 g).

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IR (Nujol) : 3300, 1780, 1720, 1660, 1640 cm⁻¹ broad s), 4.0 (3H, s), 4.24 (2H, s), NMR 6ppm (DMSO-d₆) : 3.26 (3H, s), 3.58 (2H, 5.24 (1H, d, J=SHz), 5.82 (1H, dd, J=SHz, 8Hz), 7:01 (1H, s), 9.87 (1H, d, J=8Hz)

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Example 24

7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]methylthiomethyl-3-cephem-4-carboxylic acid (syn isomer) according to the similar manner to that of Example 23. mixture of methanol (3 ml) and tetrahydrofuran (1 ml) 3-methyithiomethyl-3-cephem-4-carboxylic acid (syn formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-(0.6 g) with conc. hydrochloric acid (0.4 g) in a isomer)(0.23 g) was obtained by reacting 7-[2-(2-IR (Nujol) : 3350, 1770, 1670 cm⁻¹

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(4H, m), 3.88 (3H, s), 5.25 (1H, d, J=5Hz), 5.78 (1H, dd, J=SHz, 8Hz), 6.82 (1H, s), 7.24 (2H, broad s), 9.64 (1H, d, J=8Hz) NMR ϕ ppm (DMSO- d_{δ}) : 2.01 (3H, s), 3.2-4.1

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stirred at -20 to -15°C for 15 minutes. After the reaction N,N-dimethylformamide (2.92 ml) and phosphorus oxychloride mixture was poured into water, it was extracted with ethyl an eluent. The fractions containing the desired compound acetate. The extract was washed with an aqueous solution Removal of the solvent gave a residue (13.4 g), which was chromatographed on silica gel (100 ml) using a was added at -15°C an activated acid, which was prepared mixture of beniene and ethyl acetate (5:1 by volume) as were collected and then evaporated to dryness to obtain (3.46 ml) in a conventional manner, and the mixture was of sodium bicarbonate and an aqueous solution of sodium benzhydryl 7-[(2-formamidothiazol-4-yl)glyoxylamido]-3chloride, followed by drying over anhydrous magnesium from (2-formamidothiazol-4-yl)glycxylic acid (6.56 g), silylacetamide (18.4 g) in methylene chloride (100 ml) To a solution of benthydryl 7-amino-5-methylthio methyl.3-cephem-4-carboxylate (10 g) and trimethylmethylthiomethyl.5-cephem-4-carboxylate (7.1 g)

(1H, d, J=5Hz), 5.87 (1H, dd, J=5Hz, (1H, d, J=8Hz), 12.68 (1H, broad s) N.M.R. 6ppm (DMSO-d₆) : 1.83 (3H, s), 3.58 (2H, broad s), 3.67 (2H, broad s), 5.33 8Hz), 6.90 (1H, s), 7.40 (10H, s), 8.47 (1H, s), 8.58 (1H, s), 9.88 I.R. (Nujo1) : 3300, 1780, 1700, 1656 cm

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The following compounds were obtained by reacting 7-amino-3-substituted cephalosporanic acid derivatives with the corresponding acids according to the similar manner to that of Example 25

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Example 26

7-[(2-Aminothiazol-4-yl)glyoxylamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid.

I.R. (Nujol) : 3300, 1762, 1522 cm⁻¹

Example 2

7- [2- (2- Aminothiazol - 4-yl) - DL - glycinamido] - 3methylthiomethyl-3-cephem-4-carboxylic acid.

I.R. (Nujol) : 3300, 1755, 1686, 1600 cm⁻¹·

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Example 28

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odium chloride, and then dried over anhydrous magnesium acetate. This solution was washed with an aqueous solubryness to give a residue, which was dissolved in ethyl (2.39 g), and the mixture was stirred at ambient temperature for an hour. After the insoluble substance was (4.0 g) in methylene chloride (100 ml) and terrahydrofuran (80 ml) was added N,N'-dicyclohexylcarbodiimide emoved by filtration, the filtrate was evaporated to tion of sodium bicarbonate and an aqueous solution of butoxycarbonyl-2-(2-formamidothiazol-4-yl)-DL-glycine To a mixture of benzhydryl 7-amino-3-methylthiomethyl-3-cephem-4-carboxylate (4.92 g) and N-tertsulfate. Removal of the solvent gave benzhydryl

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DL-glycinamido}-5-methylthiomethyl-3-cephem-4-carboxylate 7. [N.terr.butoxycarbonyl-2-(2-formamidothiazol-4-yl)-

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N.M.R. $\delta ppm \; (DMSO-d_{\hat{b}}) \; : \; 1.36 \; (9H, \; s), \; 1.80 \; (3H, \; s),$ 6.90 (1H, s), 7.13 (1H, s), 7.33 (10H, 5.38 (lH, d, J=8Hz), 5.6-5.9 (lH, m), I.R. (Nujol): 5500, 1770, 1710, 1680, 1615 cm⁻¹ broad s), 8.47 (1H, s), 9.08 (1H, d, 3.58 (4H, m), 5.16 (d, J=5Hz)(1H) 5.25 (d, J=5Hz) J=8Hz)

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Example 29

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A mixture of 7-[(2-formamidothiazol-4-yl)-

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crystals in the concentrate were collected by filtration with an aqueous solution of sodium bicarbonate and then methanol (50 ml) was stirred at ambient temperature for concentrated under feduced pressure. The precipitated glyoxylamido]-3-methylthiomethyl-3-cephem-4-carboxylic The reaction mixture was adjusted to pH 5-6 methylthiomethyl-3-cephem-4-carboxylic acid (1.1 g). acid (3.0 g) and conc. hydrochloric acid (3 ml) in to give 7-[(2-aminothiazol-4-yl)glyoxylamido]-3-2 hours.

(1H, dd, J=SHz, 8Hz), 7.37 (2H, broad s), broad s), 5.22 (1H, d, JaSHz), 5.68 N.M.R. &ppm (DMSO-d₆) : 2.00 (3H, s), 3.65 (4H, 7.83 (1H, s), 9.73 (1H, d, J*8Hz) I.R. (Nujoi) : 3300, 1762, 1522 cm⁻¹

Example 30

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thloride, dried over anhydrous magnesium sulfate and then evaporated to obtain benzhydryl 7-[N-tert-butoxycarbonyl-2-(2-formamidothiazol-4-y1)-DL-glycinamido]-3-methylthiohydrofuran (25 ml) was stirred at 30 to 35°C for 5 hours. The reaction mixture was adjusted to pH 4.5 with sodium solution was washed with an aqueous solution of sodium methyl-3-cephem-4-carboxylate (9.4 g) and conc. hydrochloric acid (4.16 ml) in methanol (100 ml) and tetra-A mixture of benzhydryl 7-[N-tert-butoxycarbonyl-2-(2-aminothiazol-4-yl)-DL-glycinamido]-3-methylthiobicarbonate and then evaporated to dryness to give a residue, which was dissolved in ethyl acetate. This nethyl-3-cephem-4-carboxylate (7.4 g).

7.43 (10H, broad s), 8.93 (1H, d, J=8Hz) N.M.R. δ ppm (DMSO- d_6) : 1.40 (9H, s), 1.80 (3H, s), I.R. (Nujol) : 3300, 1772, 1716, 1685, 1623, 1244, 3.8 (4H, m), 3.0-5.4 (2H, m), 5.6-5.9 (2H, m), 6.93 (1H, s), 7.30 (1H, s), 1170, 1166 cm⁻¹

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The following compounds were obtained by reacting 7-acylamino-3-substituted cephalosporanic acid derivatives having a formamido group with hydrochloric acid according to the similar manner to that of Example 30.

7-[2-(2-Aminothiazol-4-yl)-DL-glycinamido]-3-I.R. (Nujol) : 3300, 1755, 1686, 1600 cm⁻¹ methylthiomethyl-3-cephem-4-carboxylic acid.

7-[2-(2-Aminothiazol-4-yl)-DL-glycolamido]-3-1.R. (Nujol): 3300, 1752, 1675, 1600 cm⁻¹ methylthiomethyl-3-cephem-4-carboxylic acid.

Example 33

After the solvent was removed by distillation under reduced Benzhydryl 7-[(2-formamidothiazol-4-yl)glyoxylamido]by evaporation. The residue was pulverized with diisopropyl with ethyl acetate. The extract was washed with an aqueous sodium chloride and dried over magnesium sulfate, followed ether to obtain 7-[(2-formamidothiazol-4-yl)glyoxylamido]pressure, the residue was dissolved in water, adjusted to anisole (7 ml) and trifluoroacetic acid (14 ml), and the pH 2.0 with conc. hydrochloric acid and then extracted mixture was stirred at ambient temperature for an hour dissolved in a solution of methylene chloride (70 ml), 3-methylthiomethyl-3-cephem-4-carboxylate (7,0 g) was 3-methylthiomethyl-3-cephem-4-carboxylic acid (3.3 g).

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broad s), 5.24 (1H, d, J=SHz), 5.73 (1H, dd, J=5Hz, 8Hz), 8.43 (1H, s), N.M.R. Eppm (DMSO-d₆) : 2.00 (3H, s), 3.63 (4H, 8.57 (1H, s), 9.90 (1H; d, J#8Hz), I.R. (Nujol) : 3120, 1762, 1731, 1677 cm⁻¹ 12.80 (1H, broad s)

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acid in the presence of anisole according to the similar tives having benzhydryl ester with 2,2,2.trifluoroacetic The following compounds were obtained by reacting 7-acylamino-3-substituted cephalosporanic acid derivananner to that of Example 33,

7-[(2-Aminothiazol-4-yl)glyoxylamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid.

I.R. (Nujo1) : 3300, 1762, 1522 cm⁻¹

7-[2-(2-Aminothiazo1-4-y1)-Di.-glycolamido]-3methylthiomethyl-3-cephem-4-carboxylic acid,

1.R. (Nujo1) : 3300, 1752, 1675, 1600 cm⁻¹

Example 36

(2-aminothiazol-4-yl).DL-glycinamido]-3-methylthiomethyl-3-cephem-4-carboxylate (7.0 g), anisole (7 ml) and 2,2,2tion resin "Diaion HP.20" (Trade Mark, made by Mitsubishi trifluoroacetic acid (21 ml) was stirred at 5°C for half A mixture of benzhydryl 7-[N-tert-butoxycarbonyl-2remained aqueous solution was adjusted to pH 4.2 with 5% aqueous solution was chromatographed on nonionic adsorpwater (250 ml), elution was carried out with 30% aqueous isopropyl alcohol. The fractions containing the desired compound were collected and then evaporated, followed by stance was collected by filtration and then washed with of ethyl acetate (50 ml) and water (100 ml). After the aqueous solution of sodium bicarbonate. The resultant diisopropyl ether, followed by dissolving in a mixture the aqueous layer was completely removed, and then the Chemical Industries Ltd.) (100 ml). After washing with aqueous layer was separated out, the ethyl accrate in diisopropyl ether (300 ml), and the precipitated suban hour. To the reaction mixture was added dropwise

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lyophilization to obtain 7-{2-(2-aminothiazol-4-yl)-DLglycinamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid (2.9 g).

(4H, m), 5.27 (1H, d, J=SHz), 5.50 N.M.R. 6ppm (D,0+DC1) : 2.07 (3H, s), 3.5-4.0 1.R. (Nujol): 3300, 1755, 1686, 1600 cm⁻¹ (1H, s), 5.60 (d, J*SHz) 5.72 (d, J*SHz))(1H), 7.27 (1H, s)

Example 37

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followed by lyophilization to obtain 7-[2-(2-aminothiazol-(150 mg) at 5 to 10°C, and the mixture was stirred at the (1.1 g) in methanol (80 ml) was added sodium borohydride water (100 ml), elution was carried out with 30% aqueous isopropyl alcohol. The fractions containing the desired aqueous solution was chromatographed on nonionic adsorpcompound were collected and then evaporated to dryness, residue was added water (50 ml), followed by adjusting tion resin "Diaion HP-20" (50 ml). After washing with acid, the solvent was removed by distillation. To the same temperature for half an hour. After the reaction To a solution of 7-[(2-aminothiazol-4-yl)glyoxyl. to pH 5.0 with 10% hydrochloric acid. The resultant mixture was adjusted to pH 5.0 with 101 hydrochloric amido]-3-methylthiomethyl-3-cephem-4-carboxylic acid |-yl]-DL-glycolamido]-3-methylthiomethyl-3-cephem-4carboxylic acid (0.75 g).

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(2H, broad s), 8.33 (d, J=8Hz) 8.42 (d, J=SHz)(1H) N.M.R. & ppm (DMSO-d₆) : 2.00 (3H, s), 3.48 (2H, broad s), 5.67 (2H, broad s), 4.93 5.57 (1H, m), 6.50 (1H, s), 7.03 1.R. (Nujol) : 3300, 1752, 1675, 1600 cm⁻¹ (1H, s), 5.07 (1H, d, J#SHz),

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3-cephem-4-carboxylate (4.66 g) and trimethylsilylacetamide outoxycarbonylmethoxyiminoacetamido]-3-methylthiomethyltert-butoxycarbonylmethoxyiminoacetic acid (syn isomer) sodium chloride, and then dried over magnesium sulfate, followed by evaporation under reduced pressure to give at -20°C at a time, and the mixture was stirred at the the other hand, benzhydryl 7-amino-3-methylthiomethylwas suspended in dry tetrahydrofuran (40 ml). To the solution, and the organic layer was separated, washed (4.0 g) under ice-cooling with stirring, and the mix-To the solution was added the activated acid solution (8.6 g) were dissolved in methylene chloride (50 ml). chloride (1.23 ml) and N,N-dimethylformamide (1.1 ml) Vilsmeier reagent prepared from phosphorus oxysuspension was added 2-(2-formamidothiazol-4-yl)-2-3-cephem-4-carboxylate (syn isomer)(8.0 g), mp 132ethyl acetate (200 ml) were added to the resultant same temperature for an hour. Water (100 ml) and with 5% aqueous sodium bicarbonate and an aqueous benzhydryl 7-[2-(2-formamidothiazol-4-yl)-2-tertminutes to prepare the activated acid solution. ture was stirred at the same temperature for 50

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3.60 (2H, broad s), 3.66 (2H, broad s), 4.98 7.4 (10H, m), 7.48 (1H, s), 8.54 (1H, s), \$ppm (DMSO-d6, 6): 1.47 (9H, s), 1.83 (3H, s), 5.92 (1H, dd, J=SHz, 8Hz), 6.95 (1H, s), 9.63 (1H, d, J=8Hz), 12.65 (1H, broad s) (2H, broad s),5.32 (1H, d, J=5Hz), IR (Nujol) : 3260, 1783, 1725, 1687 cm⁻¹

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methylthiomethyl-3-cephem-4-carboxylate (syn isomer) Benzhydryl 7-[2-(2-formamidothiazol-4-yl)-2benzhydryloxycarbonylmethoxyiminoacetamido]-3-

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methoxyiminoacetic acid (syn isomer)(6.18 g), phosphorus oxychloride (1.42 ml) and N,N-dimethylformamide (1.21 ml), according to a similar manner to that of Example with the activated acid solution prepared from $2 \cdot (2 -$ (7.8 g) was obtained by reacting benzhydryl 7-amino-3-methylthiomethyl-3-cephcm-4-carboxylate (4.0 g) formamidothiazol-4-yl)-2-benzhydryloxycarbonyl-38, mp 135-142°C.

6.98 (1H, s), 7.37 (20H, m), 7.50 (1H, s), 5.98 (1H, dd, J=5Hz, 8Hz), 6.95 (1H, s), NMR dppm (DMSO-d6) : 1.83 (3H, s), 3.63 (4H, m), 5.0 (2H, broad s), 5.35 (1H, d, J=5Hz), 8.57 (1H, s), 9.82 (1H, d, J=8Hz), IR (Nujo1) : 3250, 1780, 1722, 1685 cm⁻¹ 12.73 (1H, broad s)

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N,N-dimethylformamide (0.75 ml), according to a similar 2-{2-(2,2,2-trifluoroacetamido)thiazol-4-yl}acetamido] Benzhydryl 7-[2-benzhydryloxycarbonylmethoximino-3-methylthiomethyl-3-cephem-4-carboxylate (syn isomer) isomer) (3.68 g), phosphorus oxychloride (0.89 ml) and (5.6 g) was obtained by reacting benzhydryl 7-amino-3-methylthiomethyl-3-cephem-4-carboxylate (3.0 g) with the activated acid solution prepared from 2trifluoroacetamido)thiazol-4-yl]acetic acid (syn benzhydryloxycarbonylmethoximino-2-[2-(2,2,2manner to that of Example 38, mp 165-169°C.

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5.86 (1H, dd, J=SIIz, 8Hz), 6.84 (1H, s), NMR &ppm (DMSO-d6) : 2.00 (3H, s), 3.56 (4H, m). 6.88 (1H, s), 7.3 (2011, m), 9.62 (1H, IR (Nujol) : 3300, 1786, 1733, 1675, 1610 cm⁻¹ 4.84 (2H, s), 5.26 (1H, d, J=5Ht), d, J=8Hz)

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Example 41

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To a suspension of benzhydryl 7-{2-(2-

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formamidothlazol-4-yl)-2-tert-

outoxycarbonylmethoxyiminoacetamido]-3-methylthiomethyl-3-cephem-4-carboxylate (syn isomer)(8.0 g) in methanol (160 ml) was added conc. hydrochloric acid (5.6 ml), and the mixture was stirred at 35°C for an hour.

aqueous sodium chloride and dried over magnesium sulfate. 3-cephem-4-carboxylate (syn isomer)(7.0 g), mp 140-145°C. butoxycarbonylmethoxyiminoacetamido].3-methylthiomethylsaturated aqueous sodium bicarbonate. After distilling methanol under reduced pressure, the residue was dis-The resultant solution was adjusted to pH 5.0 with a solved in water (100 ml) and ethyl acetate (200 ml). The ethyl acetate layer was washed with a saturated The solvent was removed by filtration to give [R (Nujo1) : 3250, 1780, 1723, 1680 cm⁻¹ benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-tert-

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5.29 (1H, d, J=SHz), 5.87 (1H, dd, J=SHz, NMR 6ppm (DMSO-d6): 1.43 (9H, s), 1.83 (3H, s), 8Hz), 6.83 (1H, 5), 6.95 (1H, s), 3.63 (4H, m), 4.6 (2H, broad s),

7.4 (10H, m), 9.52 (1H, d, J=8Hz)

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6.93 (1H, s), 6.97 (1H, s), 7.4 (20H, m), 5.87 (1H, dd, J=5Hz, 8Hz), 6.86 (1H, s), 4.90 (2H,broad s), 5.30 (1H, d, J=5Hz), &ppm (DMSO-d6) : 1.83 (3H, s), 3.60 (4H, m), (7.5 g) with conc, hydrochloric acid (3.9 ml) accordmethylthiomethyl-3-cephem-4-carboxylate (syn isomer) methylthiomethyl-3-cephem-4-carboxylate (syn isomer) (7.0 g), mp 148-155°C, was obtained by reacting benzhydryloxycarbonylmethoxyiminoacetamido]-3benzhydryloxycarbonylmethoxyiminoacetamido]-3ing to a similar manner to that of Example 41. Benzhydryl 7-[2-(2-aminothiazol-4-y1)-2benzhydryl 7-[2-(2-formamidothiazol-4-yl)-2-

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9.67 (1H, d, J=8Hz).

7-[2-carboxymethoxyimino-2-(2-aminothiazol-4-yl)acetamido]methylthiomethyl-3-cephem-4-carboxylic acid (syn isomer) The resultant solution was adjusted to pll 2.0 with conc. filtration and dried over phosphorus pentoxide to give hydrochloric acid. The precipitates were collected by A solution of 7-[2-carboxymethoxyimino-2-{2-(2, (4.1'g) and sodium acetate (9.56 g) in water (41 ml) 3-methylthiomethyl-3-cephem-4-carboxylic acid (syn was stirred for 19.5 hours at ambient temperature. 2,2-trifluoroacetamido)thiazol-4-yl)acetamido]-3-(somer)(1.8 g), mp 173-176°C (dec.).

(1H, dd, J=SHz, 8Hz), 6.77 (1H, s), 9.45 (1H, d, J=8Hz) 4.60 (2H, broad s), 5.17 (1H,d,J=5Hz), 5.73 NMR 6ppm (DMSO-d6) : 2.00 (3H, s), 3.57 (4H, m), IR (Nujo1) : 3370, 1772, 1670 (broad) cm⁻¹

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7-{2-carboxymethoxyimino-2-{2-(2,2,2,trifluoroacetamido}carboxylic acid (syn isomer)(4.2 g), mp $183-186^{\circ}C$ (dec.). methylene chloride (11.2 ml) was added trifluoroacetic thiazol-4-yl}acetamido]-3-methylthiomethyl-3-cephem-4carboxylate (syn isomer)(5.6 g) and anisole(5.6 ml) in 1.5 hours at ambient temperature and then poured into a mixture of diisopropyl ether (400 ml) and petroleum carbonylmethoxyimino-2-{2-(2,2,2-trifluoroacetamido)acid (11,2 ml) at 10°C. The mixture was stirred for thia:ol-4-yl)acetamidd-3-methylthiomethyl-3-cephem-4-To a solution of benzhydryl 7-{2-benzhydryloxyether (100 ml). The precipitates were collected by filtration and washed with petroleum ether to give NMR 6ppm (DMSO-d6):2.00 (3H,s), 3.62 (4H, m), 4.70 (2H, s), 5.24 (1H, d, J=5Hz), IR (Nujol) : 3300, 1778, 1723, 1660 cm⁻¹

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What we claim is:

43 A compound of the formula;

$$R^{1}-A-CONH \longrightarrow S \qquad (I)$$

in which \mathbb{R}^1 is a group of the formula:

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 \mathbb{R}^3 is carboxy or a protected carboxy group, thiomethyl or lower alkenylthiomethyl, wherein R^4 is lower alkyl and R^5 is amino or a protected amino group, ${\tt R}^2$ is lower alkoxymethyl, lower alkyl-

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= $N\sim OR^6$, wherein R^6 is hydrogen, lower alkenyl, of amino, a protected amino group, hydroxy, is lower alkylene which may have a substilower alkynyl, lower alkyl, or lower alkyl selected from carboxy, a protected carboxy tuent selected from the groups consisting group, amino, a protected amino group and substituted by one or more substituent(s) oxo and a group of the formula: a heterocyclic group, and

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a pharmaceutically acceptable salt thereof. A compound of claim 1, in which (5)

the formula: $R^{1}-A-$ is a group of the formula

in which \mathbb{R}^1 is a group of the formula

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5.80 (1H, dd, J=SHz, 8Hz), 7.60 (1H, s)

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, wherein R⁵ is amino or acylamino,

R⁶ is lower alkyl, carboxy(lower)alkyl or esterified carboxy(lower)alkyl, and

 ${ t R}^3$ is carboxy or an esterified carboxy group. compound of claim 2, which is syn isomer.

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compound of claim 3, in which R⁵ is amino. 4

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m R}^2$ is lower alkoxymethyl or lower alkylthiomethyl, compound of claim 4, in which R³ is carboxy, and Š

compound of claim 5, which is selected from is lower alkyl or carboxy(lower)alkyl the group consisting of:

7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-?-{2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido}-3-methylthiomethyl-3-cephem-4-carboxylic acid,

3-methoxymethyl-3-cephem-4-carboxylic acid or its hydrochloride, and

7-{2-(2-aminothiazol-4-y1)-2-carboxymethoxyimino-

acetamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid, A compound of claim 1, in which R is a group of the formula:

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wherein R⁵ is amino or acylamino,

A is methylene, aminomethylene, acylaminomethylene, $^{\mathrm{R}^3}$ is carboxy or an esterified carboxy group. hydroxymethylene or carbonyl, and

A compound of claim 7, in which R⁵ is amino.

œ,

 R^2 is lower alkylthiomethyl, and compound of claim 8, in which

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R3 is carboxy.

A compound of claim 9, which is selected from the group consisting of:

7-[2-(2-aminothiazol-4-yl)acetamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid,

7-{2-(2-aminothiazol-4-yl)glycinamido}-3-methylhiomethyl-3-cephem-4-carboxylic acid

'-[2-(2-aminothiazol-4-yl)glycolamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid and

7-[2-(2-aminothiazol-4-yl)glyoxylamido]-3-methylthiomethy1-3-cephem-4-carboxylic acid. Ę,

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wherein R⁴ is as defined in claim 1, A compound of claim 1, in which λ^l is a group of the formula:

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A is aminomethylene or acylaminomethylene, and $^{
m R}^3$ is carboxy or an esterified carboxy group. A compound of claim 11, in which

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 R^4SO_2NH , wherein R^4 is as defined above. R^1 is a group of the formula:

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A compound of claim 12, in which

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A compound of claim 13, which is selected from the group consisting of: 3 is carboxy. 14:

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7-[2-(3-methanesulfonamidophenyl)glycinamido]-3-7-[2-(3-methanesulfonamidophenyl)glycinamido]-3-7-[2-(3-methanesulfonamidophenyl)glycinamido]-3-7-[2-(3-methanesulfonamidophenyl)glycinamido]-3allylthiomethyl-3-cephem-4-carboxylic acid or nethoxymethyl-3-cephem-4-carboxylic acid and methylthiomethyl-3-cephem-4-carboxylic acid, ethylthiomethyl-3-cephem-4-carboxylic acid, its trifluoroacetate.

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A process for preparing a compound of the formula: 15

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in which R^1 is a group of the formula:

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 ${\tt R}^3$ is carboxy or a protected carboxy group thiomethyl or lower alkenylthiomethyl, wherein ${\rm R}^4$ is lower alkyl and ${\rm R}^5$ is amino or a protected amino group, \mathbb{R}^2 is lower alkoxymethyl, lower alkyl-

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consisting of amino, a protected amino group, hydroxy, oxo and a group of the substituent selected from the groups is lower alkylene which may have a formula:

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=N-OR⁶, wherein R⁶ is hydrogen, lower alkenyl, lower alkynyl, lower alkyl, or lower alkyl substituted by one or amino, a protected amino group and a carboxy, a protected carboxy group, more substituent(s) selected from

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and pharmaceutically acceptable salt thereof, heterocyclic group, which comprises

(1): reacting a compound of the formula:

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in which R² and R³ are each as defined above. or its reactive derivative at the amino group or a salt thereof with a compound of the formula:

or a salt thereof te give a compound of the formula; in which ${ t R}^1$ and A are each as defined above, or its reactive derivative at the carboxy group

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in which R1, R2, R3 and A are each as defined

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(2) subjecting a compound of the formula; R1-A1-CONFT

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in which A^1 is lower alkylene having a protected amino group; and R^2 , R^2 a

 1 2 and 3 are each as defined above, amino-protective group to give a compound of the or a salt thereof to removal reaction of the formula:

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in which A^2 is lower alkylene having an amino group, and R^1 , R^2 and R^3 are each as defined above,

or a salt thereof; or

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(3) subjecting a compound of the formula:

in which
$$R_a^1$$
 is a group of the formula:
$$R^8 + \frac{1}{8} + \frac{1}{8} + \frac{1}{8} + \frac{1}{8} + \frac{1}{18} + \frac{1}{18$$

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 $\ensuremath{\text{R}^2}$, $\ensuremath{\text{R}^3}$ and A are each as defined above, or a salt thereof to removal reaction of the amino-protective group to give a compound of the

formula:
$$R_b^{1-A-CONH} \xrightarrow{} R^2$$

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 R^3 is a group of the formula:

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$$H_2N \xrightarrow{N} \xrightarrow{N} \qquad \text{or} \qquad H_2N \xrightarrow{N} \xrightarrow{N} \qquad , \text{ and}$$

$$R_2^2, R_3^3 \text{ and A are each as defined above,}$$
or a salt thereof; or
$$(4) \text{ subjecting a compound of the formula:}$$

(4) subjecting a compound of the formula:

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$$R^{1}$$
-A-CONH \longrightarrow R^{2}

2

in which $\overset{\text{Na}}{\bigoplus}$ is a protected carboxy group, and R¹, R² and A are each as defined above, carboxy-protective group to give a compound of or a salt thereof to removal reaction of the

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$$R^{1}-A-CONH$$

in which R^1 , R^2 and A are each as defined above, or a salt thereof; or

(5) introducing a carboxy-protective group into a compound of the formula:

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a salt thereof to give a compound of the formula: in which R¹, R² and A are each as defined above,

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$$R^1$$
-A-CONH \longrightarrow R^2

in which R^1 , R^2 , R^3_a and A are each as defined above, or a salt thereof; or

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(6) reducing a compound of the formula:

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 $R^{1}-A^{3}-CONH \longrightarrow R^{2}$ in which A_{3}^{1} is lower alkylene having an oxo group, and $R^{1}, \ R^{2} \ \text{and} \ R^{3} \ \text{are each as defined}$

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or a salt thereof to give a compound of the

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k in which A⁴ is lower alk<u>y</u>lene having a hydroxy

group, and $$\rm R^{2}$$ and $\rm R^{3}$ are each as defined above, or a salt thereof; or reacting a compound of the formula: ε,

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$$x^1$$
- CH_2COA^5 - $CONH$ \xrightarrow{S} 0 $\xrightarrow{R_3}$ R^2 is lower alkylene which may have

a group of the formula: $\texttt{=}N\texttt{-}OR^{\text{O}}$, wherein R^{O} is as defined above,

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 χ^1 is halogen, and R^2 and R^3 are each as defined above,

or a salt thereof with a compound of the formula;

H2N-G-R5

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in which $R^{\mbox{\scriptsize S}}$ is as defined above, to give a compound of the formula:

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in which R^2 , R^3 , R^5 and A^5 are each as defined above,

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or a salt thereof; or

subjecting a compound of the formula; 3

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 $R^{1}-A^{6}$ -CONH \longrightarrow 0 \longrightarrow \mathbb{R}^{2}

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in which Á⁶ is lower alkylene having a group

of the formula: =N.OR⁶,

wherein R_a^6 is lower alkyl substituted by

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protected carboxy group, and R^1 , R^2 and R^3 are each as defined above, or a salt thereof to removal reaction of the carboxy-protective group to give a compound of the formula:

$$R^{1-A^{7}}$$
-CONH R^{2} -R²

in which A^7 is lower alkylene having a group of the formula:

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=N~OR $_b^6$, wherein R_b^6 is lower alkyl sub-

stituted by carboxy, and ${\bf k}^1,\ {\bf R}^2$ and ${\bf R}^3$ are each as defined

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subjecting a compound of the formula: or a salt thereof; or

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 $^{
m R}_{
m D}^3$ in which $^{
m R}_{
m D}^3$ is lower alkoxycarbonyl substituted by protected amino and protected carboxy groups, and

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amino- and carboxy-protective groups to give a or a salt thereof to removal reaction of the compound of the formula;

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stituted by amino and carboxy, and $$\rm R^1,\,R^2$ and A are each as defined above, in which R_c^3 is lower alkoxycarbonyl sub-

(10) subjecting a compound of the formula: or a salt thereof, or

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R¹, R² and R³ are each as defined above, amino and protected carboxy groups, protected carboxy groups or lower in which A is lower alkylene having a group stituted by protected amino and amino. and carboxy-protective groups to give a alkoxycarbonyl(lower)alkyl subalkyl substituted by protected or a salt thereof to removal reaction of the of the formula: "N~OR6, wherein R6 is lower

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by amino and carboxy, and R^1 , R^2 and R^3 are each as defined above, carboxy or lower alkyl substituted of the formula: "N~OR $_d^6$, wherein R_d^6 is lower alkoxycarbonyl(lower)in which A is lower alkylene having a group alkyl substituted by amino and or a salt thereof; or

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introducing a carboxy-protective group into a compound of the formula: (11)

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$$R^{1}-A^{7}$$
-CONH $\longrightarrow R^{2}$

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in which R^1 , R^2 , R^3 and A^7 are each as deor a salt thereof to give a compound of the fined above,

in which R¹, R², R³ and A⁶ are each as or a salt thereof; or defined above,

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compound of the formula:

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reacting a compound of the formula: (17)

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formula: () , and R¹, R² and R³ are each as defined substituted by a group of the group of the £ormula: "N~OR^t in which Alo is lower alkylene having a wherein R⁶ is lower alkyl

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or a salt thereof with a compound of the

formula:

to give a compound of the formula: in which R7 is lower alkyl,

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wherein $R_{\mathbf{f}}^{\mathbf{6}}$ is lower alkyl substituted by a group of the formula: group of the formula: "N~OR¢ in which A¹¹ is lower alkylene having a

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 R^1 , R^2 and R^3 are each as defined above, wherein R^7 is as defined above,

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(13) reacting a compound of the formula: or a salt thereof; or

$$R^{1} \cdot A^{11} \cdot CONH \underset{O}{ } \longrightarrow R^{2}$$

in which R^1 , R^2 and A^{11} are each as defined

or a salt thereof with a base to give a compound of the formula:

$$R^{1}-A^{12}$$
- CONH R^{2}

substituted by a cation of the group of the formula: $=N\sim 0R_{g}^{6}$, , coo Θ , coo Θ in which A^{12} is lower alkylene having $\mathfrak a$ wherein Rg is lower alkyl defined above, and wherein R⁷ is as formula:

 R^{1} and R^{2} are each as defined above. or a salt thereof.

admixture with pharmaceutically acceptable carriers. A pharmaceutical composition comprising, as active A method for treating an infectious disease caused ingredients, the compounds of the claim 1, in bathogenic microorganisms, which comprises

A compound of the formula: human being and animals.

administering a compound of the claim 1 to infected

— СИ₂S-R^b'

in which R^A is amino or a protected amino group, R^{b^+} is lower alkenyl,

X' is -S- or -SO-, and

 ${\tt R}^3$ is carboxy or a protected carboxy group,

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and a salt thereof.

A process for preparing a compound of the formula: 19.

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-- CH2S-R^{b1}

in which R^{A} is amino or a protected amino group, R^{b} is lower alkenyl,

X is -S- or -SO-, and

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 ${ t R}^3$ is carboxy or a protected carboxy group, and a salt thereof,

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which comprises

(1) reacting a compound of the formula:

residue (-SR^b) of the compound of is as defined above, and R³ is as the formula: HS-R^b', in which R^{b'} Y is a conventional group which is capable to be replaced by the in which R^a is a protected amino group, defined above

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or a salt thereof with a compound of the formula:

Rb'-SH

or its: reactive derivative at the mercapto group in which Rb' is as defined above, to give a compound of the formula:

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in which R^a , R^b , and R^3 are each as defined above, or a salt thereof; or

reducing a compound of the formula; (2)

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in which Ra, Rb' and R3 are each as defined above, or a salt thereof to give a compound of the formula:

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in which $R^{\dot{a}},\ R^{\dot{b}}$ and $R^{\dot{3}}$ are each as defined

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(3), subjecting a compound of the formula: or a salt thereof; or

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in which R^a , R^b , and R^3 are each as defined above,

or a salt thereof to removal reaction of the amino-protective group to give a compound of the formula:

in which Rb' and R3 are each as defined above, or a salt thereof.

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